Harrison's Principles of Internal Medicine, 16th Edition
Chapter 25. Disorders of the Eye
Jonathan C. Horton

The Human Visual System

The visual system provides a supremely efficient means for the rapid assimilation of information from the environment to aid in the guidance of behavior. The act of seeing begins with the capture of images focused by the cornea and lens upon a light-sensitive membrane in the back of the eye, called the *retina*. The retina is actually part of the brain, banished to the periphery to serve as a transducer for the conversion of patterns of light energy into neuronal signals. Light is absorbed by photopigment in two types of receptors: rods and cones. In the human retina there are 100 million rods and 5 million cones. The rods operate in dim (scotopic) illumination. The cones function under daylight (photopic) conditions. The cone system is specialized for color perception and high spatial resolution. The majority of cones are located within the macula, the portion of the retina serving the central 10° of vision. In the middle of the macula a small pit termed the *fovea* , packed exclusively with cones, provides best visual acuity.

Photoreceptors hyperpolarize in response to light, activating bipolar, amacrine, and horizontal cells in the inner nuclear layer. After processing of photoreceptor responses by this complex retinal circuit, the flow of sensory information ultimately converges upon a final common pathway: the ganglion cells. These cells translate the visual image impinging upon the retina into a continuously varying barrage of action potentials that propagates along the primary optic pathway to visual centers within the brain. There are a million ganglion cells in each retina, and hence a million fibers in each optic nerve.

Ganglion cell axons sweep along the inner surface of the retina in the nerve fiber layer, exit the eye at the optic disc, and travel through the optic nerve, optic chiasm, and optic tract to reach targets in the brain. The majority of fibers synapse upon cells in the lateral geniculate body, a thalamic relay station. Cells in the lateral geniculate body project in turn to the primary visual cortex. This massive afferent retinogeniculocortical sensory pathway provides the neural substrate for visual perception. Although the lateral geniculate body is the main target of the retina, separate classes of ganglion cells project to other subcortical visual nuclei involved in different functions. Ganglion cells that mediate pupillary constriction and circadian rhythms are light sensitive, owing to a novel visual pigment, melanopsin. Pupil responses are mediated by input to the pretectal olivary nuclei in the midbrain. The pretectal nuclei send their output to the Edinger-Westphal nuclei, which in turn provide parasympathetic innervation to the iris sphincter via an interneuron in the ciliary ganglion. Circadian rhythms are timed by a retinal projection to the suprachiasmatic nucleus. Visual orientation and eye movements are served by retinal input to the superior colliculus. Gaze stabilization and optokinetic reflexes are governed by a group of small retinal targets known collectively as the *brainstem accessory optic system* .

The eyes must be rotated constantly within their orbits to place and maintain targets of visual interest upon the fovea. This activity, called *foveation* , or looking, is governed by an elaborate efferent motor system. Each eye is moved by six extraocular muscles, supplied by cranial nerves from the oculomotor (III), trochlear (IV), and abducens (VI) nuclei. Activity in these ocular motor nuclei is coordinated by pontine and midbrain mechanisms for smooth pursuit, saccades, and gaze stabilization during head and body movements. Large regions of the frontal and parietooccipital cortex control these brainstem eye movement centers by providing descending supranuclear input.

Clinical Assessment of Visual Function

Refractive State

In approaching the patient with reduced vision, the first step is to decide whether refractive error is responsible. In *emmetropia*, parallel rays from infinity are focused perfectly upon the retina. Sadly, this condition is enjoyed by only a minority of the population. In *myopia*, the globe is too long, and light rays come to a focal point in front of the retina. Near objects can be seen clearly, but distant objects require a diverging lens in front of the eye. In *hyperopia*, the globe is too short, and hence a converging lens is used to supplement the refractive power of the eye. In *astigmatism*, the corneal surface is not perfectly spherical, necessitating a cylindrical corrective lens. In recent years it has become possible to correct refractive error with the excimer laser by performing LASIK (laser in situ keratomileusis) to alter the curvature of the cornea.

With the onset of middle age, *presbyopia* develops as the lens within the eye becomes unable to increase its refractive power to accommodate upon near objects. To compensate for presbyopia, the emmetropic patient must use reading glasses. The patient already wearing glasses for distance correction usually switches to bifocals. The only exception is the myopic patient, who may achieve clear vision at near simply by removing glasses containing the distance prescription.

Refractive errors usually develop slowly and remain stable after adolescence, except in unusual circumstances. For example, the acute onset of diabetes mellitus can produce sudden myopia because of lens edema induced by hyperglycemia. Testing vision through a pinhole aperture is a useful way to screen quickly for refractive error. If the visual acuity is better through a pinhole than with the unaided eye, the patient needs a refraction to obtain best corrected visual acuity.

Visual Acuity

The Snellen chart is used to test acuity at a distance of 6 m (20 ft). For convenience, a scale version of the Snellen chart, called the Rosenbaum card, is held at 36 cm (14 in) from the patient (Fig. 25-1). All subjects should be able to read the 6/6 m (20/20 ft) line with each eye using their refractive correction, if any. Patients who need reading glasses

because of presbyopia must wear them for accurate testing with the Rosenbaum card. If 6/6 (20/20) acuity is not present in each eye, the deficiency in vision must be explained. If worse than 6/240 (20/800), acuity should be recorded in terms of counting fingers, hand motions, light perception, or no light perception. Legal blindness is defined by the Internal Revenue Service as a best corrected acuity of 6/60 (20/200) or less in the better eye, or a binocular visual field subtending 20° or less. For driving the laws vary by state, but most require a corrected acuity of 6/12 (20/40) in at least one eye. Patients with a homonymous hemianopia should not drive.


Figure 25-1 The Rosenbaum card is a miniature, scale version of the Snellen chart for testing visual acuity at near. When the visual acuity is recorded, the Snellen distance equivalent should bear a notation indicating that vision was tested at near, not at 6 m (20 ft), or else the Jaeger number system should be used to report the acuity.

Pupils

The pupils should be tested individually in dim light with the patient fixating on a distant target. If they respond briskly to light, there is no need to check the near response, because isolated loss of constriction (miosis) to accommodation does not occur. For this reason, the ubiquitous abbreviation PERRLA (pupils equal, round, and reactive to light and accommodation) implies a wasted effort with the last step. However, it is important to test the near response if the light response is poor or absent. Light-near dissociation occurs with neurosyphilis (Argyll Robertson pupil), lesions of the dorsal midbrain (obstructive hydrocephalus, pineal region tumors), and after aberrant regeneration (oculomotor nerve palsy, Adie's tonic pupil).

An eye with no light perception has no pupillary response to direct light stimulation. If the retina or optic nerve is only partially injured, the direct pupillary response will be weaker than the consensual pupillary response evoked by shining a light into the other eye. This *relative afferent pupillary defect* (Marcus Gunn pupil) can be elicited with the swinging flashlight test (Fig. 25-2). It is an extremely useful sign in retrobulbar optic neuritis and other optic nerve diseases, where it may be the sole objective evidence for disease.
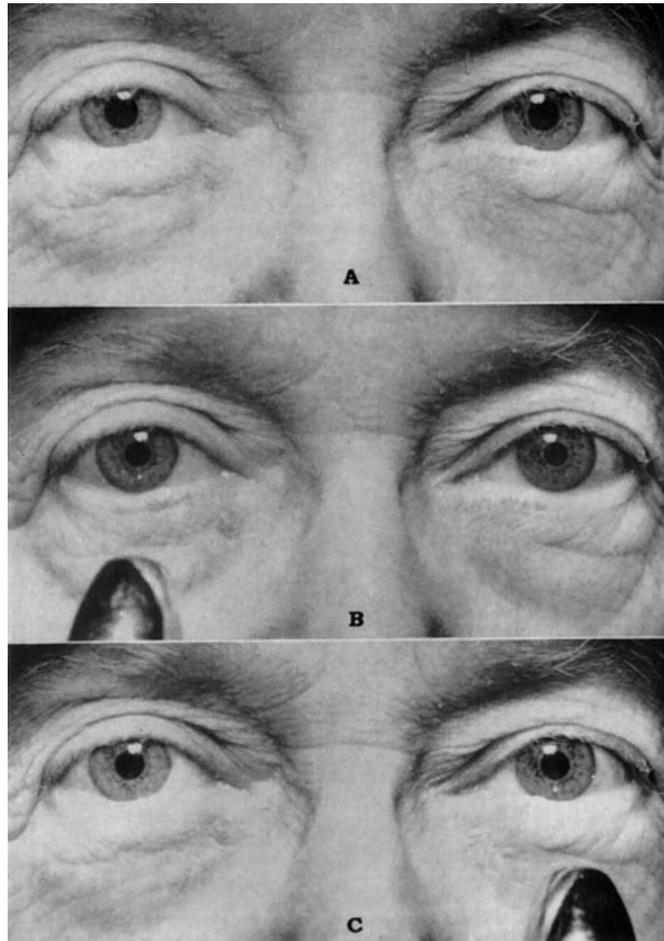
Figure 25-2 The swinging flashlight test shows a relative afferent pupil defect (Marcus Gunn pupil) in the left eye. *A*. With the patient fixating on a distant target and background lighting dim, the pupils are equal and relatively large. *B*. Shining a flashlight into the right eye evokes equal, strong constriction of both pupils. *C*. Swinging the flashlight over to the damaged left eye causes dilation of both pupils, although they remain smaller than in *A*. Swinging the flashlight back over to the healthy right eye would result in symmetric constriction back to the appearance shown in *B*. Note that the pupils always remain equal; the damage to the left retina/optic nerve is revealed by weaker bilateral pupil constriction to a flashlight in the left eye compared with the right eye.

Subtle inequality in pupil size, up to 0.5 mm, is a fairly common finding in normal persons. The diagnosis of essential or physiologic anisocoria is secure as long as the relative pupil asymmetry remains constant as ambient lighting varies. Anisocoria that increases in dim light indicates a sympathetic paresis of the iris dilator muscle. The triad of miosis with ipsilateral ptosis and anhidrosis constitutes Horner's syndrome, although

anhidrosis is an inconstant feature. Brainstem stroke, carotid dissection, or neoplasm impinging upon the sympathetic chain are occasionally identified as the cause of Horner's syndrome, but most cases are idiopathic.

Anisocoria that increases in bright light suggests a parasympathetic palsy. The first concern is an oculomotor nerve paresis. This possibility is excluded if the eye movements are full and the patient has no ptosis or diplopia. Acute pupillary dilation (mydriasis) can occur from damage to the ciliary ganglion in the orbit. Common mechanisms are infection (herpes zoster, influenza), trauma (blunt, penetrating, surgical), or ischemia (diabetes, temporal arteritis). After denervation of the iris sphincter the pupil does not respond well to light, but the response to near is often relatively intact. When the near stimulus is removed, the pupil redilates very slowly compared with the normal pupil, hence the term *tonic pupil*. In Adie's syndrome, a tonic pupil occurs in conjunction with weak or absent tendon reflexes in the lower extremities. This benign disorder, which occurs predominantly in healthy young women, is assumed to represent a mild dysautonomia. Tonic pupils are also associated with Shy-Drager syndrome, segmental hypohidrosis, diabetes, and amyloidosis. Occasionally, a tonic pupil is discovered incidentally in an otherwise completely normal, asymptomatic individual. The diagnosis is confirmed by placing a drop of dilute (0.125%) pilocarpine into each eye. Denervation hypersensitivity produces pupillary constriction in a tonic pupil, whereas the normal pupil shows no response. Pharmacologic dilation from accidental or deliberate instillation of anticholinergic agents (atropine, scopolamine drops) into the eye can also produce pupillary mydriasis. In this situation, normal strength (1%) pilocarpine causes no constriction.

Both pupils are affected equally by systemic medications. They are small with narcotic use (morphine, heroin) and large with anticholinergics (scopolamine). Parasympathetic agents (pilocarpine, demecarium bromide) used to treat glaucoma produce miosis. In any patient with an unexplained pupillary abnormality, a slit-lamp examination is helpful to exclude surgical trauma to the iris, an occult foreign body, perforating injury, intraocular inflammation, adhesions (synechia), angle-closure glaucoma, and iris sphincter rupture from blunt trauma.

Eye Movements and Alignment

Eye movements are tested by asking the patient with both eyes open to pursue a small target such as a penlight into the cardinal fields of gaze. Normal ocular versions are smooth, symmetric, full, and maintained in all directions without nystagmus. Saccades, or quick refixation eye movements, are assessed by having the patient look back and forth between two stationary targets. The eyes should move rapidly and accurately in a single jump to their target. Ocular alignment can be judged by holding a penlight directly in front of the patient at about 1 m. If the eyes are straight, the corneal light reflex will be centered in the middle of each pupil. To test eye alignment more precisely, the cover test is useful. The patient is instructed to gaze upon a small fixation target in the distance. One eye is covered suddenly while observing the second eye. If the second eye shifts to fixate upon the target, it was misaligned. If it does not move, the first eye is uncovered

and the test is repeated on the second eye. If neither eye moves, the eyes are aligned orthotropically. If the eyes are orthotropic in primary gaze but the patient complains of diplopia, the cover test should be performed with the head tilted or turned in whatever direction elicits diplopia. With practice the examiner can detect an ocular deviation (heterotropia) as small as 1 to 2° with the cover test. Deviations can be measured by placing prisms in front of the misaligned eye to determine the power required to neutralize the fixation shift evoked by covering the other eye.

Stereopsis

Stereoacuity is determined by presenting targets with retinal disparity separately to each eye using polarized images. The most popular office tests measure a range of thresholds from 800 to 40 seconds of arc. Normal stereoacuity is 40 seconds of arc. If a patient achieves this level of stereoacuity, one is assured that the eyes are aligned orthotropically and that vision is intact in each eye. Random dot stereograms have no monocular depth cues and provide an excellent screening test for strabismus and amblyopia in children.
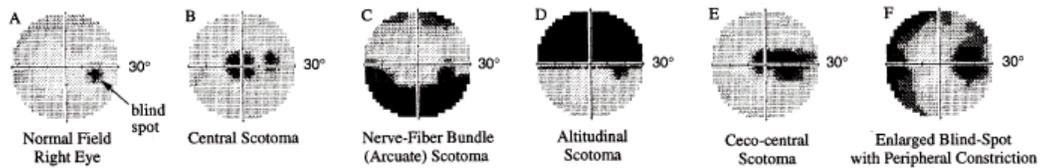
Color Vision

The retina contains three classes of cones, with visual pigments of differing peak spectral sensitivity: red (560 nm), green (530 nm), and blue (430 nm). The red and green cone pigments are encoded on the X chromosome; the blue cone pigment on chromosome 7. Mutations of the blue cone pigment are exceedingly rare. Mutations of the red and green pigments cause congenital X-linked color blindness in 8% of males. Affected individuals are not truly color blind; rather, they differ from normal subjects in how they perceive color and how they combine primary monochromatic lights to match a given color. Anomalous trichromats have three cone types, but a mutation in one cone pigment (usually red or green) causes a shift in peak spectral sensitivity, altering the proportion of primary colors required to achieve a color match. Dichromats have only two cone types and will therefore accept a color match based upon only two primary colors. Anomalous trichromats and dichromats have 6/6 (20/20) visual acuity, but their hue discrimination is impaired. Ishihara color plates can be used to detect red-green color blindness. The test plates contain a hidden number, visible only to subjects with color confusion from red-green color blindness. Because color blindness is almost exclusively X-linked, it is worth screening only male children.

The Ishihara plates are often used to detect acquired defects in color vision, although they are intended as a screening test for congenital color blindness. Acquired defects in color vision frequently result from disease of the macula or optic nerve. For example, patients with a history of optic neuritis often complain of color desaturation long after their visual acuity has returned to normal. Color blindness can also occur from bilateral strokes involving the ventral portion of the occipital lobe (cerebral achromatopsia). Such patients can perceive only shades of gray and may also have difficulty recognizing faces (prosopagnosia). Infarcts of the dominant occipital lobe sometimes give rise to color anomia. Affected patients can discriminate colors, but they cannot name them.
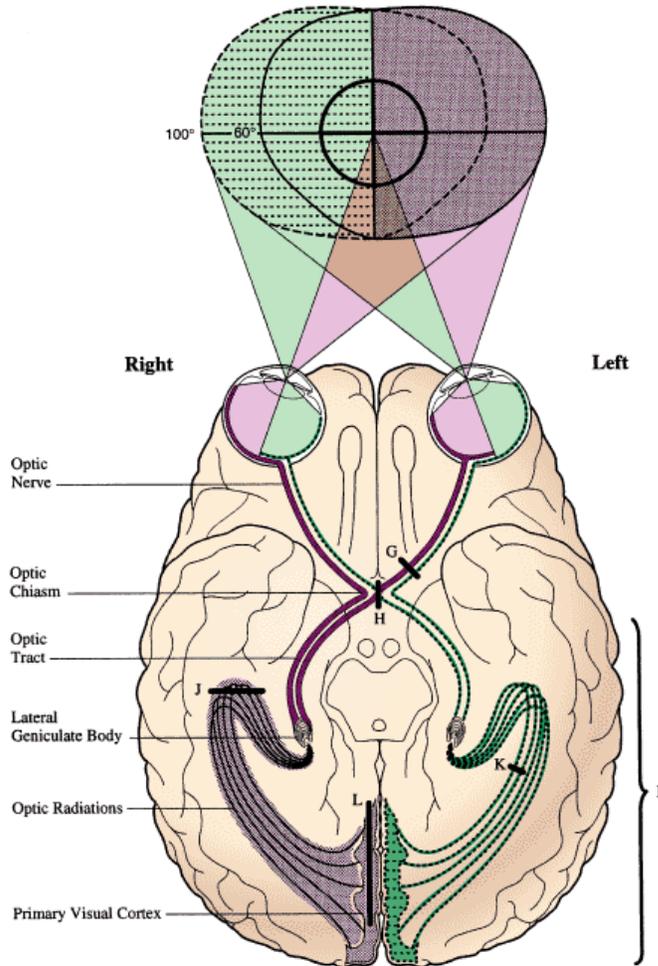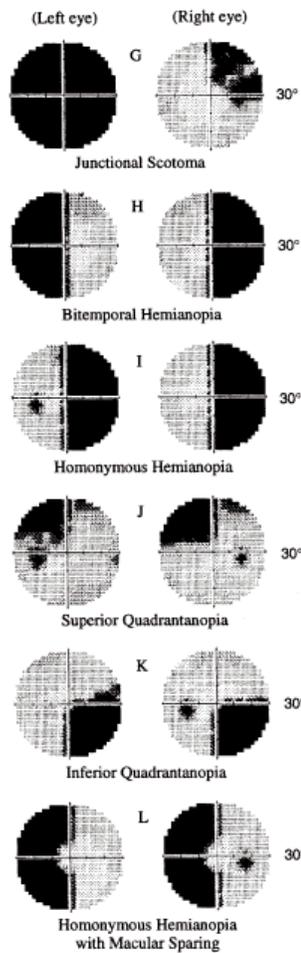
Visual Fields

Vision can be impaired by damage to the visual system anywhere from the eyes to the occipital lobes. One can localize the site of the lesion with considerable accuracy by mapping the visual field deficit by finger confrontation and then correlating it with the topographic anatomy of the visual pathway (Fig. 25-3). Quantitative visual field mapping is performed by computer-driven perimeters (Humphrey, Octopus) that present a target of variable intensity at fixed positions in the visual field (Fig. 25-3 *A*). By generating an automated printout of light thresholds, these static perimeters provide a sensitive means of detecting scotomas in the visual field. They are exceedingly useful for serial assessment of visual function in chronic diseases such as glaucoma or pseudotumor cerebri.

Monocular Prechiasmal Field Defects:

A — Normal Field Right Eye (blind spot)
B — Central Scotoma
C — Nerve-Fiber Bundle (Arcuate) Scotoma
D — Altitudinal Scotoma
E — Ceco-central Scotoma
F — Enlarged Blind-Spot with Peripheral Constriction

Binocular Chiasmal or Postchiasmal Field Defects:

(Left eye) (Right eye)

G — Junctional Scotoma
H — Bitemporal Hemianopia
I — Homonymous Hemianopia
J — Superior Quadrantanopia
K — Inferior Quadrantanopia
L — Homonymous Hemianopia with Macular Sparing

Optic Nerve
Optic Chiasm
Optic Tract
Lateral Geniculate Body
Optic Radiations
Primary Visual Cortex

Right   Left

Figure 25-3 Ventral view of the brain, correlating patterns of visual field loss with the sites of lesions in the visual pathway. The visual fields overlap partially, creating 120° of central binocular field flanked by a 40° monocular crescent on either side. The visual field maps in this figure were done with a computer-driven perimeter (Humphrey Instruments, Carl Zeiss, Inc.). It plots the retinal sensitivity to light in the central 30° using a gray scale format. Areas of visual field loss are shown in black. The examples of common monocular, prechiasmal field defects are all shown for the right eye. By convention, the visual fields are always recorded with the left eye's field on the left, and the right eye's field on the right, just as the patient sees the world.

The crux of visual field analysis is to decide whether a lesion is before, at, or behind the optic chiasm. If a scotoma is confined to one eye, it must be due to a lesion anterior to the chiasm, involving either the optic nerve or retina. Retinal lesions produce scotomas that correspond optically to their location in the fundus. For example, a superior-nasal retinal

detachment results in an inferior-temporal field cut. Damage to the macula causes a central scotoma (Fig. 25-3 *B*).

Optic nerve disease produces characteristic patterns of visual field loss. Glaucoma selectively destroys axons that enter the superotemporal or inferotemporal poles of the optic disc, resulting in arcuate scotomas shaped like a Turkish scimitar, which emanate from the blind spot and curve around fixation to end flat against the horizontal meridian (Fig. 25-3 *C*). This type of field defect mirrors the arrangement of the nerve fiber layer in the temporal retina. Arcuate or nerve fiber layer scotomas also occur from optic neuritis, ischemic optic neuropathy, optic disc drusen, and branch retinal artery or vein occlusion.

Damage to the entire upper or lower pole of the optic disc causes an altitudinal field cut that follows the horizontal meridian (Fig. 25-3 *D*). This pattern of visual field loss is typical of ischemic optic neuropathy but also occurs from retinal vascular occlusion, advanced glaucoma, and optic neuritis.

About half the fibers in the optic nerve originate from ganglion cells serving the macula. Damage to papillomacular fibers causes a cecocentral scotoma encompassing the blind spot and macula (Fig. 25-3 *E*). If the damage is irreversible, pallor eventually appears in the temporal portion of the optic disc. Temporal pallor from a cecocentral scotoma may develop in optic neuritis, nutritional optic neuropathy, toxic optic neuropathy, Leber's hereditary optic neuropathy, and compressive optic neuropathy. It is worth mentioning that the temporal side of the optic disc is slightly more pale than the nasal side in most normal individuals. Therefore, it can sometimes be difficult to decide whether the temporal pallor visible on fundus examination represents a pathologic change. Pallor of the nasal rim of the optic disc is a less equivocal sign of optic atrophy.

At the optic chiasm, fibers from nasal ganglion cells decussate into the contralateral optic tract. Crossed fibers are damaged more by compression than uncrossed fibers. As a result, mass lesions of the sellar region cause a temporal hemianopia in each eye. Tumors anterior to the optic chiasm, such as meningiomas of the tuberculum sella, produce a junctional scotoma characterized by an optic neuropathy in one eye and a superior temporal field cut in the other eye (Fig. 25-3 *G*). More symmetric compression of the optic chiasm by a pituitary adenoma (Fig. 318-4), meningioma, craniopharyngioma, glioma, or aneurysm results in a bitemporal hemianopia (Fig. 25-3 *H*). The insidious development of a bitemporal hemianopia often goes unnoticed by the patient and will escape detection by the physician unless each eye is tested separately.

It is difficult to localize a postchiasmal lesion accurately, because injury anywhere in the optic tract, lateral geniculate body, optic radiations, or visual cortex can produce a homonymous hemianopia, i.e., a temporal hemifield defect in the contralateral eye and a matching nasal hemifield defect in the ipsilateral eye (Fig. 25-3 *I*). A unilateral postchiasmal lesion leaves the visual acuity in each eye unaffected, although the patient may read the letters on only the left or right half of the eye chart. Lesions of the optic radiations tend to cause poorly matched or incongruous field defects in each eye. Damage to the optic radiations in the temporal lobe (Meyer's loop) produces a superior quadrantic

homonymous hemianopia (Fig. 25-3 *J*), whereas injury to the optic radiations in the parietal lobe results in an inferior quadrantic homonymous hemianopia (Fig. 25-3 *K*). Lesions of the primary visual cortex give rise to dense, congruous hemianopic field defects. Occlusion of the posterior cerebral artery supplying the occipital lobe is a frequent cause of total homonymous hemianopia. Some patients with hemianopia after occipital stroke have macular sparing, because the macular representation at the tip of the occipital lobe is supplied by collaterals from the middle cerebral artery (Fig. 25-3 *L*). Destruction of both occipital lobes produces cortical blindness. This condition can be distinguished from bilateral prechiasmal visual loss by noting that the pupil responses and optic fundi remain normal.

Red or Painful Eye

Corneal Abrasions

These are seen best by placing a drop of fluorescein in the eye and looking with the slit lamp using a cobalt-blue light. A penlight with a blue filter will suffice if no slit lamp is available. Damage to the corneal epithelium is revealed by yellow fluorescence of the exposed basement membrane underlying the epithelium. It is important to check for foreign bodies. To search the conjunctival fornices, the lower lid should be pulled down and the upper lid everted. A foreign body can be removed with a moistened cotton-tipped applicator after placing a drop of topical anesthetic, such as proparacaine, in the eye. Alternatively, it may be possible to flush the foreign body from the eye by irrigating copiously with saline or artificial tears. If the corneal epithelium has been abraded, antibiotic ointment and a patch should be applied to the eye. A drop of an intermediate-acting cycloplegic, such as cyclopentolate hydrochloride 1%, helps to reduce pain by relaxing the ciliary body. The eye should be reexamined the next day. Minor abrasions may not require patching and cycloplegia.

Subconjunctival Hemorrhage

This results from rupture of small vessels bridging the potential space between the episclera and conjunctiva. Blood dissecting into this space can produce a spectacular red eye, but vision is not affected and the hemorrhage resolves without treatment. Subconjunctival hemorrhage is usually spontaneous but can occur from blunt trauma, eye rubbing, or vigorous coughing. Occasionally it is a clue to an underlying bleeding disorder.

Pinguecula

This is a small, raised conjunctival nodule at the temporal or nasal limbus. In adults such lesions are extremely common and have little significance, unless they become inflamed (pingueculitis). A *pterygium* resembles a pinguecula but has crossed the limbus to

encroach upon the corneal surface. Removal is justified when symptoms of irritation or blurring develop, but recurrence is a common problem.

Blepharitis

This refers to inflammation of the eyelids. The most common form occurs in association with acne rosacea or seborrheic dermatitis. The eyelid margins are usually colonized heavily by staphylococci. Upon close inspection, they appear greasy, ulcerated, and crusted with scaling debris that clings to the lashes. Treatment consists of warm compresses, strict eyelid hygiene, and topical antibiotics such as *erythromycin* . An external *hordeolum* (sty) is caused by staphylococcal infection of the superficial accessory glands of Zeis or Moll located in the eyelid margins. An internal hordeolum occurs after suppurative infection of the oil-secreting meibomian glands within the tarsal plate of the eyelid. Systemic antibiotics, usually tetracyclines, are sometimes necessary for treatment of meibomian gland inflammation (meibomitis) or chronic, severe blepharitis. A *chalazion* is a painless, granulomatous inflammation of a meibomian gland that produces a pealike nodule within the eyelid. It can be incised and drained, or injected with glucocorticoids. Basal cell, squamous cell, or meibomian gland carcinoma should be suspected for any nonhealing, ulcerative lesion of the eyelids.

Dacrocystitis

An inflammation of the lacrimal drainage system, this can produce epiphora (tearing) and ocular injection. Gentle pressure over the lacrimal sac evokes pain and reflux of mucus or pus from the tear puncta. Dacrocystitis usually occurs after obstruction of the lacrimal system. It is treated with topical and systemic antibiotics, followed by probing or surgery to reestablish patency. *Entropion* (inversion of the eyelid) or *ectropion* (sagging or eversion of the eyelid) can also lead to epiphora and ocular irritation.

Conjunctivitis

This is the most common cause of a red, irritated eye. Pain is minimal, and the visual acuity is reduced only slightly. The most common viral etiology is adenovirus infection. It causes a watery discharge, mild foreign-body sensation, and photophobia. Bacterial infection tends to produce a more mucopurulent exudate. Mild cases of infectious conjunctivitis are usually treated empirically with broad-spectrum topical ocular antibiotics, such as sulfacetamide 10%, polymixin-bacitracin-neomycin, or trimethoprim-polymixin combination. Smears and cultures are usually reserved for severe, resistant, or recurrent cases of conjunctivitis. To prevent contagion, patients should be admonished to wash their hands frequently, not to touch their eyes, and to avoid direct contact with others.

Allergic Conjunctivitis

This condition is extremely common and often mistaken for infectious conjunctivitis. Itching, redness, and epiphora are typical. The palpebral conjunctiva may become

hypertropic with giant excrescences called cobblestone papillae. Irritation from contact lenses or any chronic foreign body can also induce formation of cobblestone papillae. *Atopic conjunctivitis* occurs in subjects with atopic dermatitis or asthma. Symptoms caused by allergic conjunctivitis can be alleviated with cold compresses, topical vasoconstrictors, antihistamines, and mast-cell stabilizers such as cromolyn sodium. Topical glucocorticoid solutions provide dramatic relief of immune-mediated forms of conjunctivitis, but their long-term use is ill-advised because of the complications of glaucoma, cataract, and secondary infection. Topical nonsteroidal anti-inflammatory agents (NSAIDs) such as ketorolac tromethamine are a better alternative.

Keratoconjunctivitis Sicca

Also known as dry eye, it produces a burning, foreign-body sensation, injection, and photophobia. In mild cases the eye appears surprisingly normal, but tear production measured by wetting of a filter paper (Schirmer strip) is deficient. A variety of systemic drugs, including antihistaminic, anticholinergic, and psychotropic medications, result in dry eye by reducing lacrimal secretion. Disorders that involve the lacrimal gland directly, such as sarcoidosis or Sjögren's syndrome, also cause dry eye. Patients may develop dry eye after radiation therapy if the treatment field includes the orbits. Problems with ocular drying are also common after lesions affecting cranial nerves V or VII. Corneal anesthesia is particularly dangerous, because the absence of a normal blink reflex exposes the cornea to injury without pain to warn the patient. Dry eye is managed by frequent and liberal application of artificial tears and ocular lubricants. In severe cases the tear puncta can be plugged or cauterized to reduce lacrimal outflow.

Keratitis

This is a threat to vision because of the risk of corneal clouding, scarring, and perforation. Worldwide, the two leading causes of blindness from keratitis are trachoma from chlamydial infection and vitamin A deficiency related to malnutrition. In the United States, contact lenses play a major role in corneal infection and ulceration. They should not be worn by anyone with an active eye infection. In evaluating the cornea, it is important to differentiate between a superficial infection (*keratoconjunctivitis*) and a deeper, more serious ulcerative process. The latter is accompanied by greater visual loss, pain, photophobia, redness, and discharge. Slit-lamp examination shows disruption of the corneal epithelium, a cloudy infiltrate or abscess in the stroma, and an inflammatory cellular reaction in the anterior chamber. In severe cases, pus settles at the bottom of the anterior chamber, giving rise to a hypopyon. Immediate empirical antibiotic therapy should be initiated after corneal scrapings are obtained for Gram's stain, Giemsa stain, and cultures. Fortified topical antibiotics are most effective, supplemented with subconjunctival antibiotics as required. A fungal etiology should always be considered in the patient with keratitis. Fungal infection is common in warm humid climates, especially after penetration of the cornea by plant or vegetable material.

Herpes Simplex

The *herpes viruses* are a major cause of blindness from keratitis. Most adults in the United States have serum antibodies to herpes simplex, indicating prior viral infection (Chap. 163). Primary ocular infection is generally caused by herpes simplex type 1, rather than type 2. It manifests as a unilateral follicular blepharoconjunctivitis, easily confused with adenoviral conjunctivitis unless telltale vesicles appear on the periocular skin or conjunctiva. A dendritic pattern of corneal epithelial ulceration revealed by fluorescein staining is pathognomonic for herpes infection but is seen in only a minority of primary infections. Recurrent ocular infection arises from reactivation of the latent herpes virus. Viral eruption in the corneal epithelium may result in the characteristic herpes dendrite. Involvement of the corneal stroma produces edema, vascularization, and iridocyclitis. Herpes keratitis is treated with topical antiviral agents, cycloplegics, and oral acyclovir. Topical glucocorticoids are effective in mitigating corneal scarring but must be used with extreme caution because of the danger of corneal melting and perforation. Topical glucocorticoids also carry the risk of prolonging infection and inducing glaucoma.

Herpes Zoster

Herpes zoster from reactivation of latent varicella (chickenpox) virus causes a dermatomal pattern of painful vesicular dermatitis. Ocular symptoms can occur after zoster eruption in any branch of the trigeminal nerve but are particularly common when vesicles form on the nose, reflecting nasociliary (V1) nerve involvement (Hutchinson's sign). Herpes zoster ophthalmicus produces corneal dendrites, which can be difficult to distinguish from those seen in herpes simplex. Stromal keratitis, anterior uveitis, raised intraocular pressure, ocular motor nerve palsies, acute retinal necrosis, and postherpetic scarring and neuralgia are other common sequelae. Herpes zoster ophthalmicus is treated with antiviral agents and cycloplegics. In severe cases, glucocorticoids may be added to prevent permanent visual loss from corneal scarring.

Episcleritis

This is an inflammation of the episclera, a thin layer of connective tissue between the conjunctiva and sclera. Episcleritis resembles conjunctivitis but is a more localized process and discharge is absent. Most cases of episcleritis are idiopathic, but some occur in the setting of an autoimmune disease. *Scleritis* refers to a deeper, more severe inflammatory process, frequently associated with a connective tissue disease such as rheumatoid arthritis, lupus erythematosus, polyarteritis nodosa, Wegener's granulomatosis, or relapsing polychondritis. The inflammation and thickening of the sclera can be diffuse or nodular. In anterior forms of scleritis, the globe assumes a violet hue and the patient complains of severe ocular tenderness and pain. With posterior scleritis the pain and redness may be less marked, but there is often proptosis, choroidal effusion, reduced motility, and visual loss. Episcleritis and scleritis should be treated with NSAIDs. If these agents fail, topical or even systemic glucocorticoid therapy may be necessary, especially if an underlying autoimmune process is active.

Uveitis

Involving the anterior structures of the eye, this is also called *iritis* or *iridocyclitis* . The diagnosis requires slit-lamp examination to identify inflammatory cells floating in the aqueous humor or deposited upon the corneal endothelium (keratic precipitates). Anterior uveitis develops in sarcoidosis, ankylosing spondylitis, juvenile rheumatoid arthritis, inflammatory bowel disease, psoriasis, Reiter's syndrome, and Behçet's disease. It is also associated with herpes infections, syphilis, Lyme disease, onchocerciasis, tuberculosis, and leprosy. Although anterior uveitis can occur in conjunction with many diseases, no cause is found to explain the majority of cases. For this reason, laboratory evaluation is usually reserved for patients with recurrent or severe anterior uveitis. Treatment is aimed at reducing inflammation and scarring by judicious use of topical glucocorticoids. Dilation of the pupil reduces pain and prevents the formation of synechiae.

Posterior Uveitis

This is diagnosed by observing inflammation of the vitreous, retina, or choroid on fundus examination. It is more likely than anterior uveitis to be associated with an identifiable systemic disease. Some patients have panuveitis, or inflammation of both the anterior and posterior segments of the eye. Posterior uveitis is a manifestation of autoimmune diseases such as sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome, and inflammatory bowel disease (Fig. 25-4). It also accompanies diseases such as toxoplasmosis, onchocerciasis, cysticercosis, coccidioidomycosis, toxocariasis, and histoplasmosis; infections caused by organisms such as *Candida*, *Pneumocystis carinii*, *Cryptococcus*, *Aspergillus*, herpes, and cytomegalovirus (see Fig. 166-1); and other diseases such as syphilis, Lyme disease, tuberculosis, cat-scratch disease, Whipple's disease, and brucellosis. In multiple sclerosis, chronic inflammatory changes can develop in the extreme periphery of the retina (pars planitis or intermediate uveitis).

Figure 25-4 Retinal vasculitis, uveitis, and hemorrhage in a 32-year-old woman with Crohn's disease. Note that the veins are frosted with a white exudate. Visual acuity improved from 20/400 to 20/20 following treatment with intravenous methylprednisolone.

Acute Angle-Closure Glaucoma

This is a rare and frequently misdiagnosed cause of a red, painful eye. Susceptible eyes have a shallow anterior chamber, either because the eye has a short axial length (hyperopia) or a lens enlarged by the gradual development of cataract. When the pupil becomes mid-dilated, the peripheral iris blocks aqueous outflow via the anterior chamber angle and the intraocular pressure rises abruptly, producing pain, injection, corneal edema, obscurations, and blurred vision. In some patients, ocular symptoms are overshadowed by nausea, vomiting, or headache, prompting a fruitless workup for abdominal or neurologic disease. The diagnosis is made by measuring the intraocular pressure during an acute attack or by observing a narrow chamber angle by means of a specially mirrored contact lens. Acute angle closure is treated with oral or intravenous acetazolamide, topical beta blockers, prostaglandin analogues, α_2-adrenergic agonists, and pilocarpine to induce miosis. If these measures fail, a laser can be used to create a hole in the peripheral iris to relieve pupillary block. Many physicians are reluctant to dilate patients routinely for fundus examination because they fear precipitating an angle-closure glaucoma. The risk is actually remote and more than outweighed by the potential benefit to patients of discovering a hidden fundus lesion visible only through a fully dilated pupil. Moreover, a single attack of angle closure after pharmacologic dilation rarely causes any permanent damage to the eye and serves as an inadvertent provocative test to identify patients with narrow angles who would benefit from prophylactic laser iridectomy.

Endophthalmitis

This occurs from bacterial, viral, fungal, or parasitic infection of the internal structures of the eye. It is usually acquired by hematogenous seeding from a remote site. Chronically ill, diabetic, or immunosuppressed patients, especially those with a history of indwelling intravenous catheters or positive blood cultures, are at greatest risk for endogenous endophthalmitis. Although most patients have ocular pain and injection, visual loss is sometimes the only symptom. Septic emboli, from a diseased heart valve or a dental abscess, that lodge in the retinal circulation can give rise to endophthalmitis. White-centered retinal hemorrhages (Roth's spots) are considered pathognomonic for subacute bacterial endocarditis, but they also appear in leukemia, diabetes, and many other conditions. Endophthalmitis also occurs as a complication of ocular surgery, occasionally months or even years after the operation. An occult penetrating foreign body or unrecognized trauma to the globe should be considered in any patient with unexplained intraocular infection or inflammation.

Transient or Sudden Visual Loss

Amaurosis Fugax

This term refers to a transient ischemic attack of the retina (Chap. 349). Because neural tissue has a high rate of metabolism, interruption of blood flow to the retina for more than a few seconds results in *transient monocular blindness*, a term used interchangeably with amaurosis fugax. Patients describe a rapid fading of vision like a curtain descending, sometimes affecting only a portion of the visual field. Amaurosis fugax usually occurs from an embolus that becomes stuck within a retinal arteriole (Fig. 25-5). If the embolus breaks up or passes, flow is restored and vision returns quickly to normal without permanent damage. With prolonged interruption of blood flow, the inner retina suffers infarction. Ophthalmoscopy reveals zones of whitened, edematous retina following the distribution of branch retinal arterioles. Complete occlusion of the central retinal artery produces arrest of blood flow and a milky retina with a cherry-red fovea (Fig. 25-6). Emboli are composed of either cholesterol (Hollenhorst plaque), calcium, or platelet-fibrin debris. The most common source is an atherosclerotic plaque in the carotid artery or aorta, although emboli can also arise from the heart, especially in patients with diseased valves, atrial fibrillation, or wall motion abnormalities.
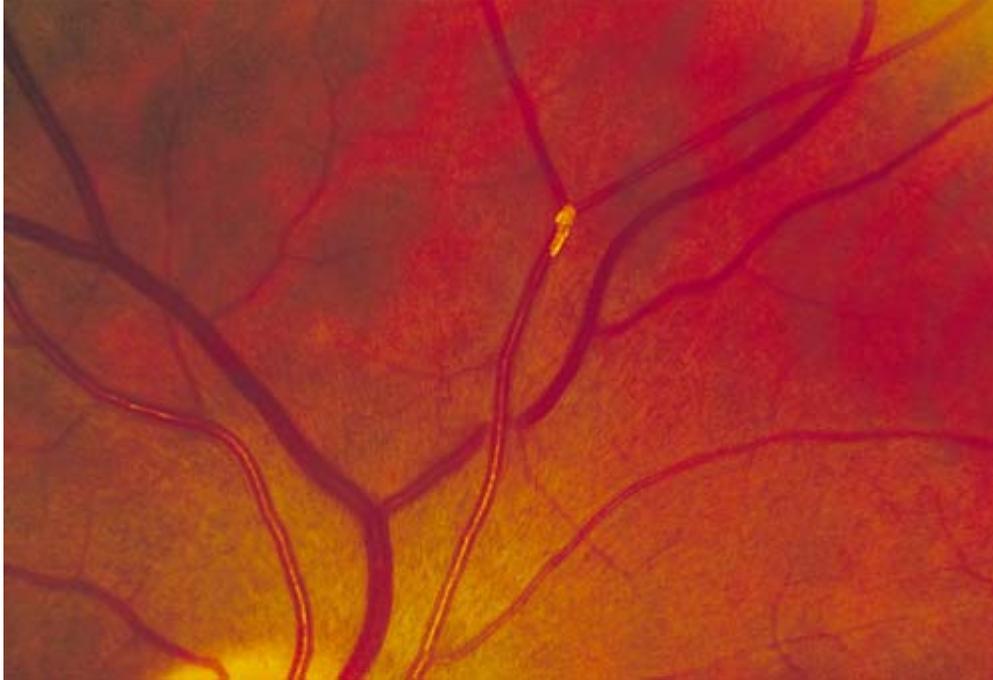
Figure 25-5 Hollenhorst plaque lodged at the bifurcation of a retinal arteriole proves that a patient is shedding emboli from either the carotid artery, great vessels, or heart.
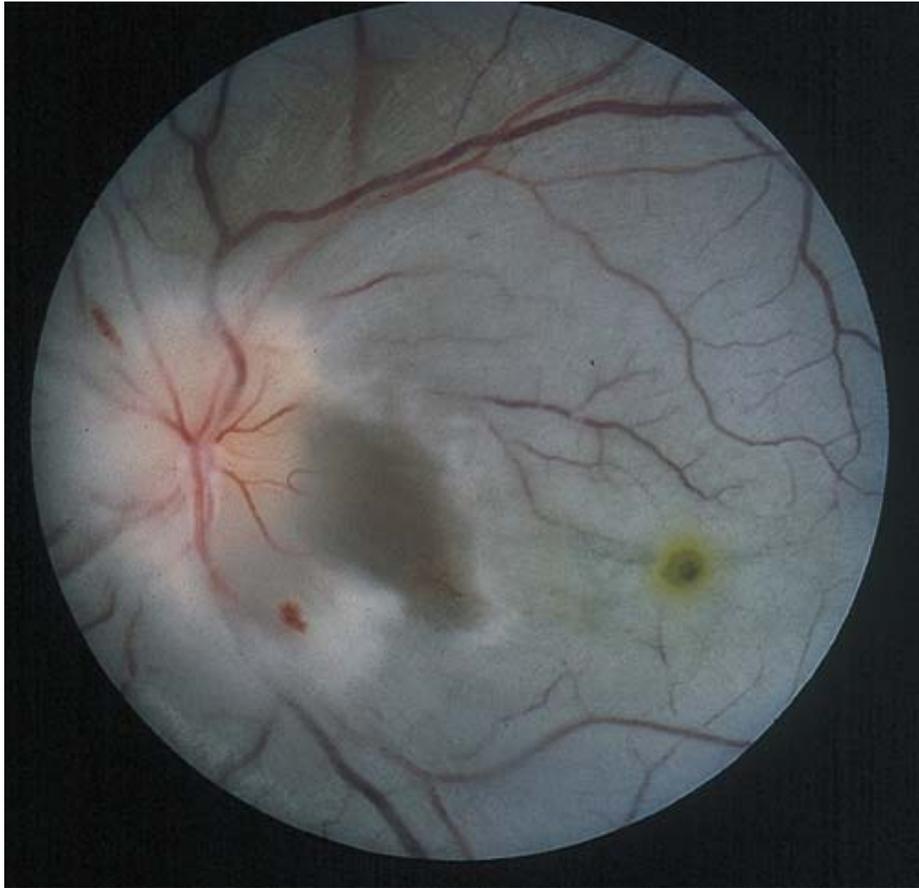
Figure 25-6 Central retinal artery occlusion combined with ischemic optic neuropathy in a 19-year-old woman with an elevated titer of anticardiolipin antibodies. Note the orange dot (rather than cherry red) corresponding to the fovea and the spared patch of retina just temporal to the optic disc.

In rare instances, amaurosis fugax occurs from low central retinal artery perfusion pressure in a patient with a critical stenosis of the ipsilateral carotid artery and poor collateral flow via the circle of Willis. In this situation, amaurosis fugax develops when there is a dip in systemic blood pressure or a slight worsening of the carotid stenosis. Sometimes there is contralateral motor or sensory loss, indicating concomitant hemispheric cerebral ischemia.

Retinal arterial occlusion also occurs rarely in association with retinal migraine, lupus erythematosus, anticardiolipin antibodies (Fig. 25-6), anticoagulant deficiency states (protein S, protein C, and antithrombin III deficiency), pregnancy, intravenous drug abuse, blood dyscrasias, dysproteinemias, and temporal arteritis.

Marked *systemic hypertension* causes sclerosis of retinal arterioles, splinter hemorrhages, focal infarcts of the nerve fiber layer (cotton-wool spots), and leakage of lipid and fluid (hard exudate) into the macula (Fig. 25-7). In hypertensive crisis, sudden visual loss can result from vasospasm of retinal arterioles and retinal ischemia. In addition, acute hypertension may produce visual loss from ischemic swelling of the optic disc. Patients

with acute hypertensive retinopathy should be treated by lowering the blood pressure. However, the blood pressure should not be reduced precipitously, because there is a danger of optic disc infarction from sudden hypoperfusion.

Figure 25-7 Hypertensive retinopathy with scattered flame (splinter) hemorrhages and cotton wool spots (nerve fiber layer infarcts) in a patient with headache and a blood pressure of 234/120.

Impending *branch* or *central retinal vein occlusion* can produce prolonged visual obscurations that resemble those described by patients with amaurosis fugax. The veins appear engorged and phlebitic, with numerous retinal hemorrhages (Fig. 25-8). In some patients, venous blood flow recovers spontaneously, while others evolve a frank obstruction with extensive retinal bleeding ("blood and thunder" appearance), infarction, and visual loss. Venous occlusion of the retina is often idiopathic, but hypertension, diabetes, and glaucoma are prominent risk factors. Polycythemia, thrombocythemia, or other factors leading to an underlying hypercoagulable state should be corrected; aspirin treatment may be beneficial.
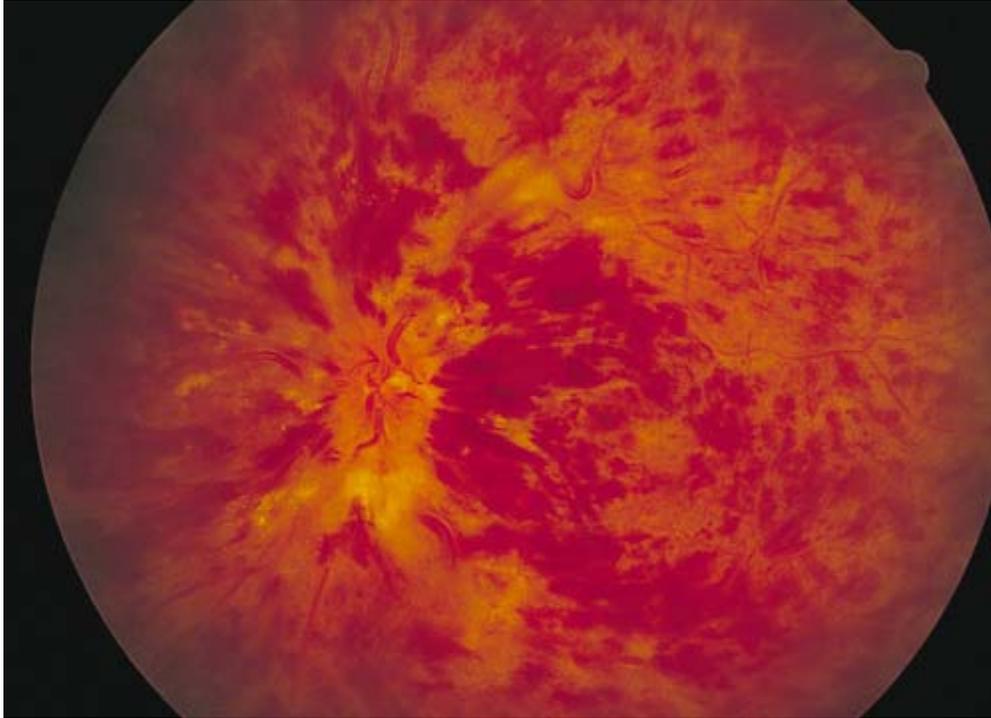
Figure 25-8 Central retinal vein occlusion can produce massive retinal hemorrhage ("blood and thunder"), ischemia, and vision loss.

Anterior Ischemic Optic Neuropathy (Aion)

This is caused by insufficient blood flow through the posterior ciliary arteries supplying the optic disc. It produces painless, monocular visual loss that is usually sudden, although some patients have progressive worsening. The optic disc appears swollen and surrounded by nerve fiber layer splinter hemorrhages (Fig. 25-9). AION is divided into two forms: arteritic and nonarteritic. The nonarteritic form of AION is most common. No specific cause can be identified, although diabetes and hypertension are frequent risk factors. No treatment is available. About 5% of patients, especially those over age 60, develop the arteritic form of AION in conjunction with giant cell (temporal) arteritis (Chap. 306). It is urgent to recognize arteritic AION so that high doses of glucocorticoids can be instituted immediately to prevent blindness in the second eye. Symptoms of polymyalgia rheumatica may be present; the sedimentation rate and C-reactive protein level are usually elevated. In a patient with visual loss from suspected arteritic AION, temporal artery biopsy is mandatory to confirm the diagnosis. Glucocorticoids should be started immediately, without waiting for the biopsy to be completed. The diagnosis of arteritic AION is difficult to sustain in the face of a negative temporal artery biopsy, but such cases do occur.
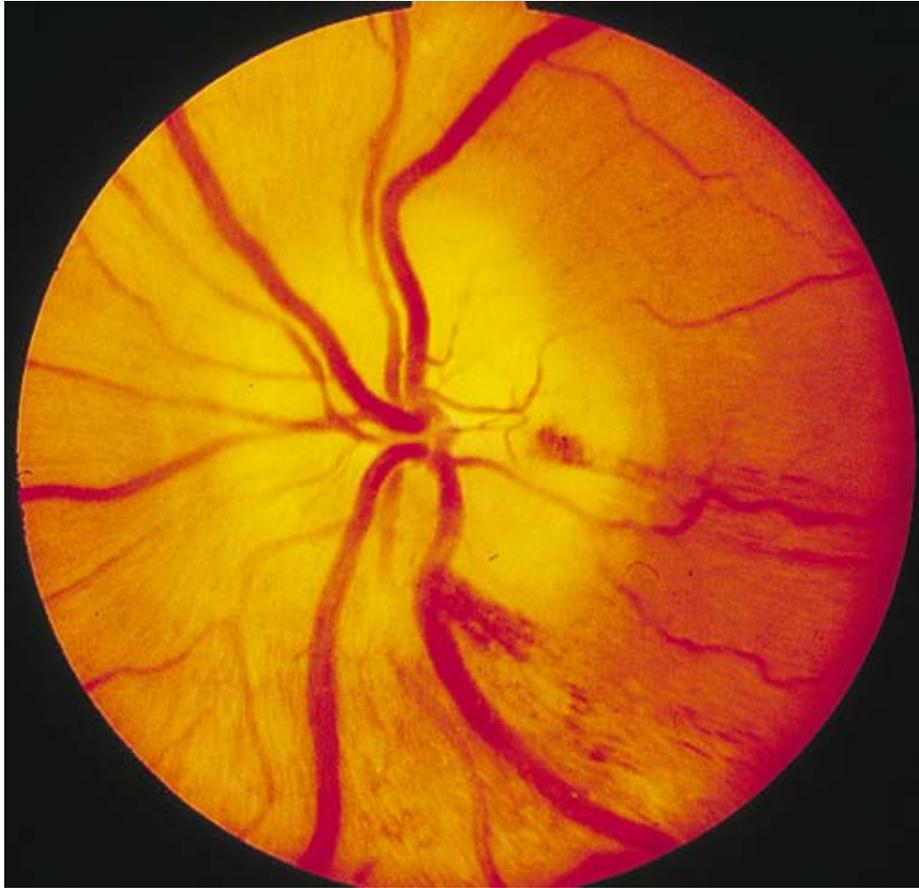
Figure 25-9 Anterior ischemic optic neuropathy from temporal arteritis in a 78-year-old woman with pallid disc swelling, hemorrhage, visual loss, myalgia, and an erythrocyte sedimentation rate of 86 mm/h.

Posterior Ischemic Optic Neuropathy

This is an infrequent cause of acute visual loss, induced by the combination of severe anemia and hypotension. Cases have been reported after major blood loss during surgery, exsanguinating trauma, gastrointestinal bleeding, and renal dialysis. The fundus usually appears normal, although optic disc swelling develops if the process extends far enough anteriorly. Vision can be salvaged in some patients by prompt blood transfusion and reversal of hypotension.

Optic Neuritis

This is a common inflammatory disease of the optic nerve. In the Optic Neuritis Treatment Trial (ONTT), the mean age of patients was 32 years, 77% were female, 92% had ocular pain (especially with eye movements), and 35% had optic disc swelling. In most patients, the demyelinating event was retrobulbar and the ocular fundus appeared normal on initial examination (Fig. 25-10), although optic disc pallor slowly developed over subsequent months.

Figure 25-10 Retrobulbar optic neuritis is characterized by a normal fundus examination initially, hence the rubric, "the doctor sees nothing, and the patient sees nothing." Optic atrophy develops after severe or repeated attacks.

Virtually all patients experience a gradual recovery of vision after a single episode of optic neuritis, even without treatment. This rule is so reliable that failure of vision to improve after a first attack of optic neuritis casts doubt upon the original diagnosis. Treatment with high-dose intravenous methylprednisolone (250 mg every 6 h for 3 days) followed by oral prednisone (1 mg/kg per day for 11 days) makes no difference in final acuity (measured 6 months after the attack), but the recovery of visual function occurs more rapidly.

For some patients, optic neuritis remains an isolated event. However, the ONTT showed that the 5-year cumulative probability of developing clinically definite multiple sclerosis following optic neuritis is 30%. In patients with two or more demyelinating plaques on brain magnetic resonance (MR) imaging, treatment with interferon beta-1a can retard the development of more lesions. In summary, an MR scan is recommended in every patient with a first attack of optic neuritis. When visual loss is severe (worse than 20/100), treatment with intravenous followed by oral glucocorticoids hastens recovery. If multiple lesions are present on the MR scan, treatment with interferon beta-1a should be broached with the patient.

Leber's Hereditary Optic Neuropathy

This is a disease of young men, characterized by gradual painless, severe, central visual loss in one eye, followed weeks or months later by the same process in the other eye. Acutely, the optic disc appears mildly plethoric with surface capillary telangiectases, but no vascular leakage on fluorescein angiography. Eventually optic atrophy ensues. Leber's optic neuropathy is caused by a point mutation at codon 11778 in the mitochondrial gene encoding nicotinamide adenine dinucleotide dehydrogenase (NADH) subunit 4. Additional mutations responsible for the disease have been identified, most in mitochondrial genes encoding proteins involved in electron transport. Mitochondrial mutations causing Leber's neuropathy are inherited from the mother by all her children, but usually only sons develop symptoms. There is no treatment.

Toxic Optic Neuropathy

This can result in acute visual loss with bilateral optic disc swelling and central or cecocentral scotomas. Such cases have been reported to result from exposure to ethambutol, methyl alcohol (moonshine), ethylene glycol (antifreeze), or carbon monoxide. In toxic optic neuropathy, visual loss can also develop gradually and produce optic atrophy (Fig. 25-11) without a phase of acute optic disc edema. Many agents have been implicated as a cause of toxic optic neuropathy, but the evidence supporting the association for many is weak. The following is a partial list of potential offending drugs or toxins: disulfiram, ethchlorvynol, chloramphenicol, amiodarone, monoclonal anti-CD3 antibody, ciprofloxacin, digitalis, streptomycin, lead, arsenic, thallium, D-penicillamine, isoniazid, emetine, and sulfonamides. Deficiency states, induced either by starvation, malabsorption, or alcoholism, can lead to insidious visual loss. Thiamine, vitamin B_{12}, and folate levels should be checked in any patient with unexplained, bilateral central scotomas and optic pallor.
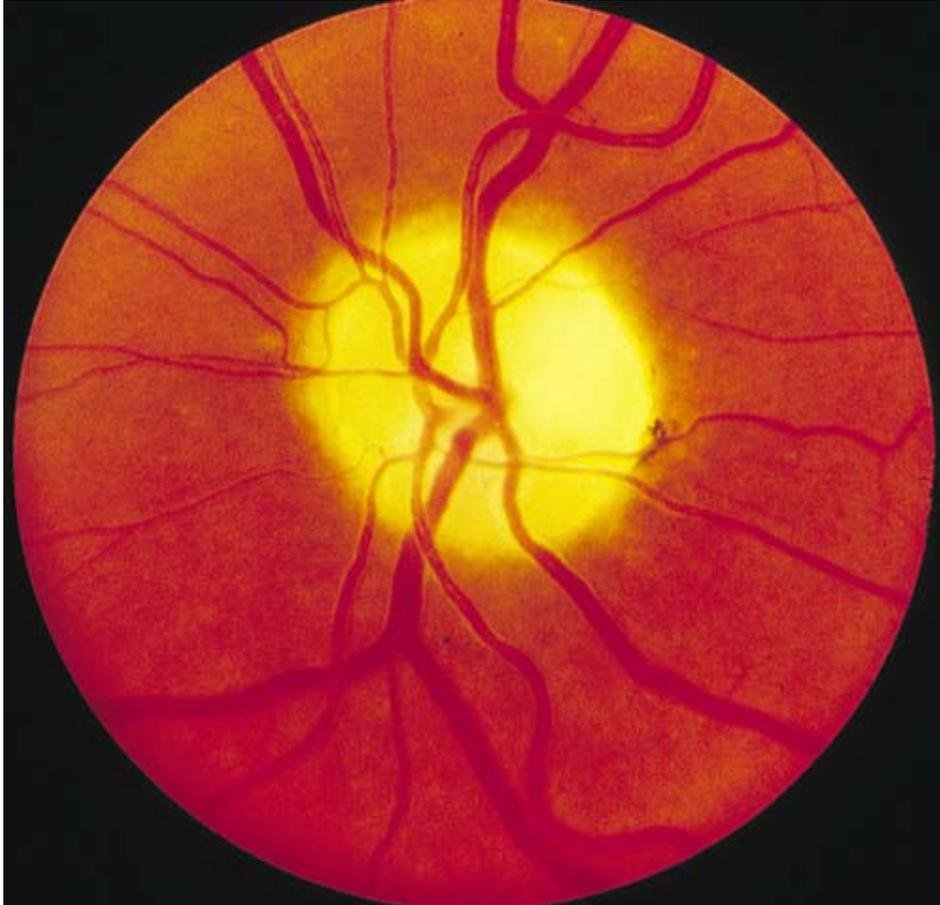
Figure 25-11 Optic atrophy is not a specific diagnosis, but refers to the combination of optic disc pallor, arteriolar narrowing, and nerve fiber layer destruction produced by a host of eye diseases, especially optic neuropathies.

Papilledema

This connotes bilateral optic disc swelling from raised intracranial pressure (Fig. 25-12). Headache is a frequent, but not invariable, accompaniment. All other forms of optic disc swelling, e.g., from optic neuritis or ischemic optic neuropathy, should be called "optic disc edema." This convention is arbitrary but serves to avoid confusion. Often it is difficult to differentiate papilledema from other forms of optic disc edema by fundus examination alone. Transient visual obscurations are a classic symptom of papilledema. They can occur in only one eye or simultaneously in both eyes. They usually last seconds but can persist longer if the papilledema is fulminant. Obscurations follow abrupt shifts in posture or happen spontaneously. When obscurations are prolonged or spontaneous, the papilledema is more threatening. Visual acuity is not affected by papilledema unless the papilledema is severe, long-standing, or accompanied by macular edema and hemorrhage. Visual field testing shows enlarged blind spots and peripheral constriction (Fig. 25-3 *F*). With unremitting papilledema, peripheral visual field loss progresses in an insidious fashion while the optic nerve develops atrophy. In this setting, reduction of optic disc swelling is an ominous sign of a dying nerve rather than an encouraging indication of resolving papilledema.

Figure 25-12 Papilledema means optic disc edema from raised intracranial pressure. This obese young women with pseudotumor cerebri was misdiagnosed as a migraineur until fundus examination was performed, showing optic disc elevation, hemorrhages, and cotton wool spots.

Evaluation of papilledema requires neuroimaging to exclude an intracranial lesion. MR angiography is appropriate in selected cases to search for a dural venous sinus occlusion or an arteriovenous shunt. If neuroradiologic studies are negative, the subarachnoid opening pressure should be measured by lumbar puncture. An elevated pressure, with normal cerebrospinal fluid, points by exclusion to the diagnosis of *pseudotumor cerebri* (idiopathic intracranial hypertension). The majority of patients are young, female, and obese. Treatment with a carbonic anhydrase inhibitor such as acetazolamide lowers intracranial pressure by reducing the production of cerebrospinal fluid. Weight reduction is vital but often unsuccessful. If acetazolamide and weight loss fail, and visual field loss is progressive, a shunt should be performed without delay to prevent blindness. Occasionally, emergency surgery is required for sudden blindness caused by fulminant papilledema.

Optic Disc Drusen

These are refractile deposits within the substance of the optic nerve head (Fig. 25-13). They are unrelated to drusen of the retina, which occur in age-related macular degeneration. Optic disc drusen are most common in people of northern European descent. Their diagnosis is obvious when they are visible as glittering particles upon the surface of the optic disc. However, in many patients they are hidden beneath the surface,

producing pseudo-papilledema. It is important to recognize optic disc drusen to avoid an unneccessary evaluation for papilledema. Ultrasound or computed tomography (CT) scanning is sensitive for detection of buried optic disc drusen because they contain calcium. In most patients, optic disc drusen are an incidental, innocuous finding, but they can produce visual obscurations. On perimetry they give rise to enlarged blind spots and arcuate scotomas from damage to the optic disc. With increasing age, drusen tend to become more exposed on the disc surface as optic atrophy develops. Hemorrhage, choroidal neovascular membrane, and AION are more likely to occur in patients with optic disc drusen. No treatment is available.

Figure 25-13 Optic disc drusen are calcified deposits of unknown etiology within the optic disc. They are sometimes confused with papilledema.

Vitreous Degeneration

This occurs in all individuals with advancing age, leading to visual symptoms. Opacities develop in the vitreous, casting annoying shadows upon the retina. As the eye moves, these distracting "floaters" move synchronously, with a slight lag caused by inertia of the vitreous gel. Vitreous traction upon the retina causes mechanical stimulation, resulting in perception of flashing lights. This photopsia is brief and confined to one eye, in contrast to the bilateral, prolonged scintillations of cortical migraine. Contraction of the vitreous can result in sudden separation from the retina, heralded by an alarming shower of floaters and photopsia. This process, known as *vitreous detachment* , is a frequent involutional event in the elderly. It is not harmful unless it damages the retina. A careful examination of the dilated fundus is important in any patient complaining of floaters or photopsia to search for peripheral tears or holes. If such a lesion is found, laser application or cryotherapy can forestall a retinal detachment. Occasionally a tear ruptures a retinal blood vessel, causing vitreous hemorrhage and sudden loss of vision. On

attempted ophthalmoscopy the fundus is hidden by a dark red haze of blood. Ultrasound is required to examine the interior of the eye for a retinal tear or detachment. If the hemorrhage does not resolve spontaneously, the vitreous can be removed surgically. Vitreous hemorrhage also occurs from the fragile neovascular vessels that proliferate on the surface of the retina in diabetes, sickle cell anemia, and other ischemic ocular diseases.

Retinal Detachment

This produces symptoms of floaters, flashing lights, and a scotoma in the peripheral visual field corresponding to the detachment (Fig. 25-14). If the detachment includes the fovea, there is an afferent pupil defect and the visual acuity is reduced. In most eyes, retinal detachment starts with a hole, flap, or tear in the peripheral retina (rhegmatogenous retinal detachment). Patients with peripheral retinal thinning (lattice degeneration) are particularly vulnerable to this process. Once a break has developed in the retina, liquified vitreous is free to enter the subretinal space, separating the retina from the pigment epithelium. The combination of vitreous traction upon the retinal surface and passage of fluid behind the retina leads inexorably to detachment. Patients with a history of myopia, trauma, or prior cataract extraction are at greatest risk for retinal detachment. The diagnosis is confirmed by ophthalmoscopic examination of the dilated eye.
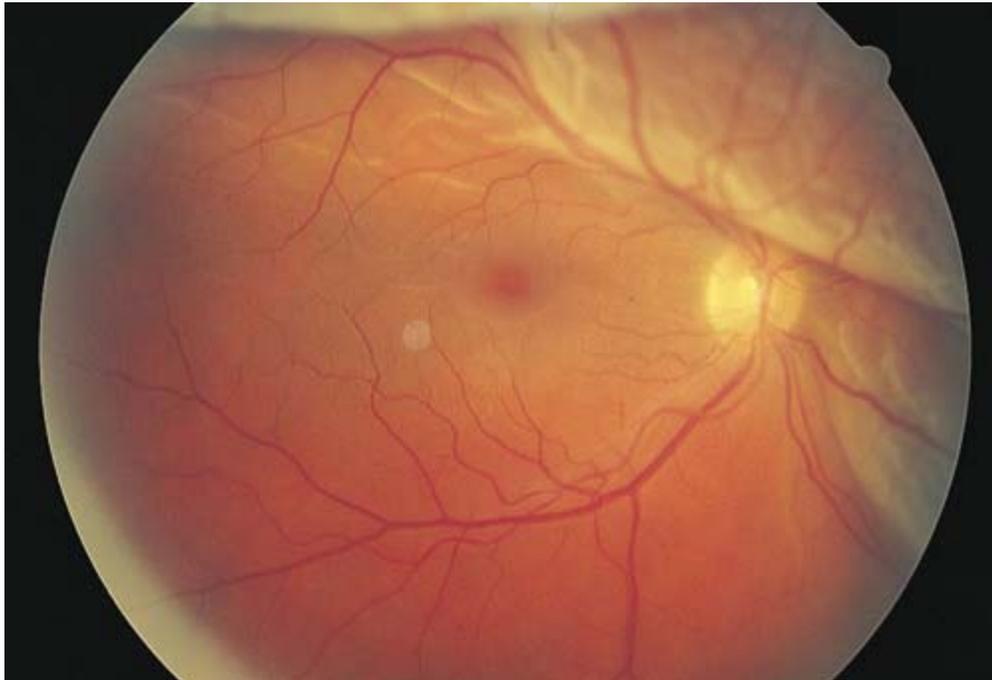
Figure 25-14 Retinal detachment appears as an elevated sheet of retinal tissue with folds. In this patient the fovea was spared, so acuity was normal, but a superior detachment produced an inferior scotoma.

Classic Migraine

See also Chap. 14. This usually occurs with a visual aura lasting about 20 min. In a typical attack, a small central disturbance in the field of vision marches toward the periphery, leaving a transient scotoma in its wake. The expanding border of migraine scotoma has a scintillating, dancing, or zig-zag edge, resembling the bastions of a fortified city, hence the term *fortification spectra* . Patients' descriptions of fortification spectra vary widely and can be confused with amaurosis fugax. Migraine patterns usually last longer and are perceived in both eyes, whereas amaurosis fugax is briefer and occurs in only one eye. Migraine phenomena also remain visible in the dark or with the eyes closed. Generally they are confined to either the right or left visual hemifield, but sometimes both fields are involved simultaneously. Patients often have a long history of stereotypic attacks. After the visual symptoms recede, headache develops in most patients.

Transient Ischemic Attacks

Vertebrobasilar insufficiency may result in acute homonymous visual symptoms. Many patients mistakenly describe symptoms in their left or right eye, when in fact they are occurring in the left or right hemifield of both eyes. Interruption of blood supply to the visual cortex causes a sudden fogging or graying of vision, occasionally with flashing lights or other positive phenomena that mimic migraine. Cortical ischemic attacks are briefer in duration than migraine, occur in older patients, and are not followed by headache. There may be associated signs of brainstem ischemia, such as diplopia, vertigo, numbness, weakness, or dysarthria.

Stroke

This occurs when interruption of blood supply from the posterior cerebral artery to the visual cortex is prolonged. The only finding on examination is a homonymous visual field defect that stops abruptly at the vertical meridian. Occipital lobe stroke is usually due to thrombotic occlusion of the vertebrobasilar system, embolus, or dissection. Lobar hemorrhage, tumor, abscess, and arteriovenous malformation are other common causes of hemianopic cortical visual loss.

Factitious (Functional, Nonorganic) Visual Loss

This is claimed by hysterics or malingerers. The latter comprise the vast majority, seeking sympathy, special treatment, or financial gain by feigning loss of sight. The diagnosis is suspected when the history is atypical, physical findings are lacking or contradictory, inconsistencies emerge on testing, and a secondary motive can be identified. In our litigious society, the fraudulent pursuit of recompense has spawned an epidemic of factitious visual loss.

Chronic Visual Loss

Cataract

This is a clouding of the lens sufficient to reduce vision. Most cataracts develop slowly as a result of aging, leading to gradual impairment of vision. The formation of cataract occurs more rapidly in patients with a history of ocular trauma, uveitis, or diabetes mellitus. Cataracts are acquired in a variety of genetic diseases, such as myotonic dystrophy, neurofibromatosis type 2, and galactosemia. Radiation therapy and glucocorticoid treatment can induce cataract as a side effect. The cataracts associated with radiation or glucocorticoids have a typical posterior subcapsular location. Cataract can be detected by noting an impaired red reflex when viewing light reflected from the fundus with an ophthalmoscope or by examining the dilated eye using the slit lamp.

The only treatment for cataract is surgical extraction of the opacified lens. Over a million cataract operations are performed each year in the United States. The operation is generally done under local anesthesia on an outpatient basis. A plastic or silicone intraocular lens is placed within the empty lens capsule in the posterior chamber, substituting for the natural lens and leading to rapid recovery of sight. More than 95% of patients who undergo cataract extraction can expect an improvement in vision. In many patients, the lens capsule remaining in the eye after cataract extraction eventually turns cloudy, causing a secondary loss of vision. A small opening is made in the lens capsule with a laser to restore clarity.

Glaucoma

This is a slowly progressive, insidious optic neuropathy, usually associated with chronic elevation of intraocular pressure. In Americans of African descent it is the leading cause of blindness. The mechanism whereby raised intraocular pressure injures the optic nerve is not understood. Axons entering the inferotemporal and superotemporal aspects of the optic disc are damaged first, producing typical nerve fiber bundle or arcuate scotomas on perimetric testing. As fibers are destroyed, the neural rim of the optic disc shrinks and the physiologic cup within the optic disc enlarges (Fig. 25-15). This process is referred to as pathologic "cupping." The cup-to-disc diameter is expressed as a ratio, e.g., 0.2/1. The cup-to-disc ratio ranges widely in normal individuals, making it difficult to diagnose glaucoma reliably simply by observing an unusually large or deep optic cup. Careful documentation of serial examinations is helpful. In the patient with physiologic cupping, the large cup remains stable, whereas in the patient with glaucoma it expands relentlessly over the years. Detection of visual field loss by computerized perimetry also contributes to the diagnosis. Finally, most patients with glaucoma have raised intraocular pressure. However, many patients with typical glaucomatous cupping and visual field loss have intraocular pressures that apparently never exceed the normal limit of 20 mmHg (so-called low-tension glaucoma).

Figure 25-15 Glaucoma results in "cupping" as the neural rim is destroyed and the central cup becomes enlarged and excavated. The cup-to-disc ratio is about 0.7/1.0 in this patient.

In acute angle-closure glaucoma, the eye is red and painful due to abrupt, severe elevation of intraocular pressure. Such cases account for only a handful of patients with glaucoma. Most patients with glaucoma have open, anterior chamber angles. The cause of raised intraocular pressure in open angle glaucoma is unknown but is associated with gene mutations in the heritable forms.

Glaucoma is usually painless (except in angle-closure glaucoma). Foveal acuity is spared until end-stage disease is reached. For these reasons, severe and irreversible damage can occur before either the patient or physician recognizes the diagnosis. Screening of patients for glaucoma by noting the cup-to-disc ratio on ophthalmoscopy and by measuring intraocular pressure is vital. Glaucoma is treated with topical adrenergic agonists, cholinergic agonists, beta blockers, and prostaglandin analogues. Occasionally, systemic absorption of beta blocker from eye drops can be sufficient to cause side effects of bradycardia, hypotension, heart block, bronchospasm, or depression. Topical or oral carbonic anhydrase inhibitors are used to lower intraocular pressure by reducing aqueous production. Laser treatment of the trabecular meshwork in the anterior chamber angle improves aqueous outflow from the eye. If medical or laser treatments fail to halt optic nerve damage from glaucoma, a filter must be constructed surgically (trabeculectomy) to release aqueous from the eye in a controlled fashion.

Macular Degeneration

This is a major cause of gradual, painless, bilateral central visual loss in the elderly. The old term, "senile macular degeneration," misinterpreted by many patients as an unflattering reference, has been replaced with "age-related macular degeneration." It occurs in a nonexudative (dry) form and an exudative (wet) form. The nonexudative process begins with the accumulation of extracellular deposits, called drusen, underneath the retinal pigment epithelium. On ophthalmoscopy, they are pleomorphic but generally appear as small discrete yellow lesions clustered in the macula (Fig. 25-16). With time they become larger, more numerous, and confluent. The retinal pigment epithelium becomes focally detached and atrophic, causing visual loss by interfering with photoreceptor function. Treatment with vitamins C and E, beta carotene, and zinc may retard dry macular degeneration.

Figure 25-16 Age-related macular degeneration begins with the accumulation of drusen within the macula. They appear as scattered yellow subretinal deposits.

Exudative macular degeneration, which develops in only a minority of patients, occurs when neovascular vessels from the choroid grow through defects in Bruch's membrane into the potential space beneath the retinal pigment epithelium. Leakage from these vessels produces elevation of the retina and pigment epithelium, with distortion (metamorphopsia) and blurring of vision. Although onset of these symptoms is usually gradual, bleeding from subretinal choroidal neovascular membranes sometimes causes acute visual loss. The neovascular membranes can be difficult to see on fundus

examination because they are beneath the retina. Fluorescein or indocyanine green angiography is extremely useful for their detection. In some patients, prompt laser ablation of choroidal neovascular membranes seen on fluorescein angiography can halt the exudative process. However, the neovascular membranes frequently recur, requiring constant vigilance and repeated photocoagulation.

Major or repeated hemorrhage under the retina from neovascular membranes results in fibrosis, development of a round (disciform) macular scar, and permanent loss of central vision. Surgical attempts to remove subretinal membranes in age-related macular degeneration have not improved vision in most patients. However, outcomes have been more encouraging for patients with choroidal neovascular membranes from ocular histoplasmosis syndrome.

Central Serous Chorioretinopathy

This primarily affects males between the ages of 20 and 50. Leakage of serous fluid from the choroid causes small, localized detachment of the retinal pigment epithelium and the neurosensory retina. These detachments produce acute or chronic symptoms of metamorphopsia and blurred vision when the macula is involved. They are difficult to visualize with a direct ophthalmoscope because the detached retina is transparent and only slightly elevated. Diagnosis of central serous chorioretinopathy is made easily by fluorescein angiography, which shows dye streaming into the subretinal space. The cause of central serous chorioretinopathy is unknown. Symptoms may resolve spontaneously if the retina reattaches, but recurrent detachment is common. Laser photocoagulation has benefited some patients with this condition.

Diabetic Retinopathy

A rare disease until 1921, when the discovery of insulin resulted in a dramatic improvement in life expectancy for patients with diabetes mellitus, it is now a leading cause of blindness in the United States. The retinopathy of diabetes takes years to develop but eventually appears in nearly all cases. Regular surveillance of the dilated fundus is crucial for any patient with diabetes. In advanced diabetic retinopathy, the proliferation of neovascular vessels leads to blindness from vitreous hemorrhage, retinal detachment, and glaucoma (see Fig. 323-9). These complications can be avoided in most patients by administration of panretinal laser photocoagulation at the appropriate point in the evolution of the disease. ***For further discussion of the manifestations and management of diabetic retinopathy, see Chap. 323.***

Retinitis Pigmentosa

This is a general term for a disparate group of rod and cone dystrophies characterized by progressive night blindness, visual field constriction with a ring scotoma, loss of acuity, and an abnormal electroretinogram (ERG). It occurs sporadically or in an autosomal recessive, dominant, or X-linked pattern. Irregular black deposits of clumped pigment in the peripheral retina, called *bone spicules* because of their vague resemblance to the

spicules of cancellous bone, give the disease its name (Fig. 25-17). The name is actually a misnomer because retinitis pigmentosa is not an inflammatory process. Most cases are due to a mutation in the gene for rhodopsin, the rod photopigment, or in the gene for peripherin, a glycoprotein located in photoreceptor outer segments. Vitamin A (15,000 IU/day) slightly retards the deterioration of the ERG in patients with retinitis pigmentosa but has no beneficial effect on visual acuity or fields. Some forms of retinitis pigmentosa occur in association with rare, hereditary systemic diseases (olivopontocerebellar degeneration, Bassen-Kornzweig disease, Kearns-Sayre syndrome, Refsum's disease). Chronic treatment with chloroquine, hydroxychloroquine, and phenothiazines (especially thioridazine) can produce visual loss from a toxic retinopathy that resembles retinitis pigmentosa.
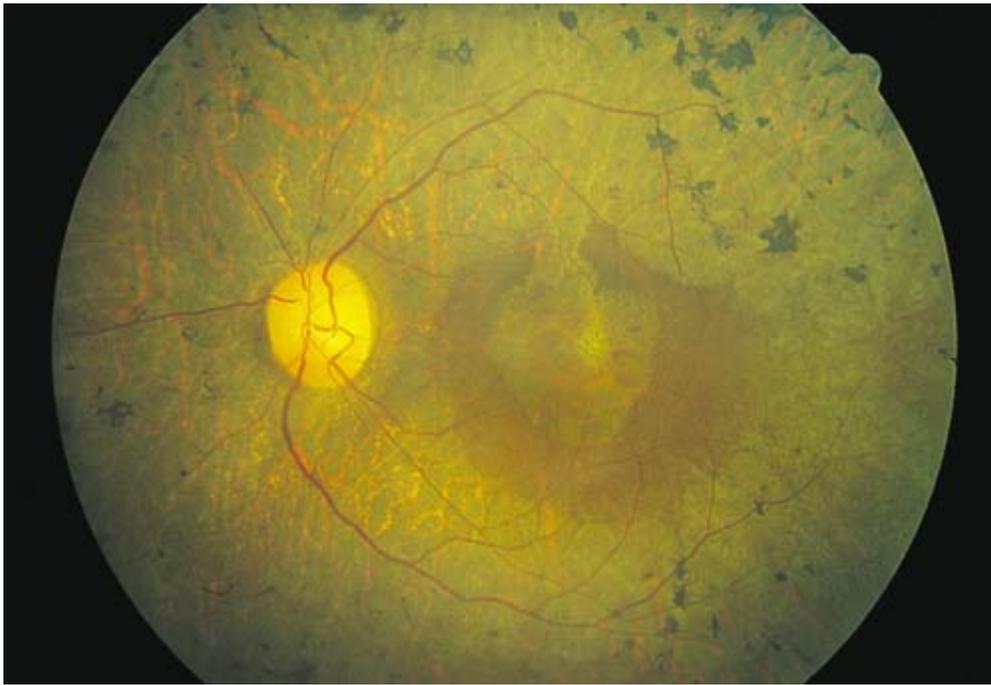
Figure 25-17 Retinitis pigmentosa with black clumps of pigment in the retinal periphery known as "bone spicules." There is also atrophy of the retinal pigment epithelium, making the vasculature of the choroid easily visible.

Epiretinal Membrane

This is a fibrocellular tissue that grows across the inner surface of the retina, causing metamorphopsia and reduced visual acuity from distortion of the macula. A crinkled, cellophane-like membrane is visible on the retinal examination. Epiretinal membrane is most common in patients over 50 years of age and is usually unilateral. Most cases are idiopathic, but some occur as a result of hypertensive retinopathy, diabetes, retinal detachment, or trauma. When visual acuity is reduced to the level of about 6/24 (20/80), vitrectomy and surgical peeling of the membrane to relieve macular puckering are recommended. Contraction of an epiretinal membrane sometimes gives rise to a *macular hole* . Most macular holes, however, are caused by local vitreous traction within the fovea. Vitrectomy can improve acuity in selected cases.

Melanoma and Other Tumors

Melanoma is the most common primary tumor of the eye (Fig. 25-18). It causes photopsia, an enlarging scotoma, and loss of vision. A small melanoma is often difficult to differentiate from a benign choroidal nevus. Serial examinations are required to document a malignant pattern of growth. Treatment of melanoma is controversial. Options include enucleation, local resection, and irradiation. *Metastatic tumors* to the eye outnumber primary tumors. Breast and lung carcinoma have a special propensity to spread to the choroid or iris. Leukemia and lymphoma also commonly invade ocular tissues. Sometimes their only sign on eye examination is cellular debris in the vitreous, which can masquerade as a chronic posterior uveitis. *Retrobulbar tumor* of the optic nerve (meningioma, glioma) or *chiasmal tumor* (pituitary adenoma, meningioma) produces gradual visual loss with few objective findings, except for optic disc pallor. Rarely, sudden expansion of a pituitary adenoma from infarction and bleeding (*pituitary apoplexy*) causes acute retrobulbar visual loss, with headache, nausea, and ocular motor nerve palsies. In any patient with visual field loss or optic atrophy, CT or MR scanning should be considered if the cause remains unknown after careful review of the history and thorough examination of the eye.

Figure 25-18 Melanoma of the choroid, appearing as an elevated dark mass in the inferior temporal fundus, just encroaching upon the fovea.

Proptosis

When the globes appear asymmetric, the clinician must first decide which eye is abnormal. Is one eye recessed within the orbit (*enophthalmos*) or is the other eye protuberant (*exophthalmos*, or *proptosis*)? A small globe or a Horner's syndrome can give the appearance of enophthalmos. True enophthalmos occurs commonly after trauma, from atrophy of retrobulbar fat, or fracture of the orbital floor. The position of the eyes within the orbits is measured using a Hertel exophthalmometer, a hand-held instrument that records the position of the anterior corneal surface relative to the lateral orbital rim. If this instrument is not available, relative eye position can be judged by bending the patient's head forward and looking down upon the orbits. A proptosis of only 2 mm in one eye is detectable from this perspective. The development of proptosis implies a space-occupying lesion in the orbit, and usually warrants CT or MR imaging.

Graves' Ophthalmopathy

This is the leading cause of proptosis in adults (Chap. 320). The proptosis is often asymmetric and can even appear to be unilateral. Orbital inflammation and engorgement of the extraocular muscles, particularly the medial rectus and the inferior rectus, account for the protrusion of the globe. Corneal exposure, lid retraction, conjunctival injection, restriction of gaze, diplopia, and visual loss from optic nerve compression are cardinal symptoms. Graves' ophthalmopathy is treated with oral prednisone (60 mg/d) for 1 month, followed by a taper over several months, topical lubricants, eyelid surgery, eye muscle surgery, or orbital decompression. Radiation therapy is not effective.

Orbital Pseudotumor

This is an idiopathic, inflammatory orbital syndrome, frequently confused with Graves' ophthalmopathy. Symptoms are pain, limited eye movements, proptosis, and congestion. Evaluation for sarcoidosis, Wegener's granulomatosis, and other types of orbital vasculitis or collagen-vascular disease is negative. Imaging often shows swollen eye muscles (orbital myositis) with enlarged tendons. By contrast, in Graves' ophthalmopathy the tendons of the eye muscles are usually spared. The Tolosa-Hunt syndrome may be regarded as an extension of orbital pseudotumor through the superior orbital fissure into the cavernous sinus. The diagnosis of orbital pseudotumor is difficult. Biopsy of the orbit frequently yields nonspecific evidence of fat infiltration by lymphocytes, plasma cells, and eosinophils. A dramatic response to a therapeutic trial of systemic glucocorticoids indirectly provides the best confirmation of the diagnosis.

Orbital Cellulitis

This causes pain, lid erythema, proptosis, conjunctival chemosis, restricted motility, decreased acuity, afferent pupillary defect, fever, and leukocytosis. It often arises from the paranasal sinuses, especially by contiguous spread of infection from the ethmoid sinus through the lamina papyracea of the medial orbit. A history of recent upper respiratory tract infection, chronic sinusitis, thick mucous secretions, or dental disease is

significant in any patient with suspected orbital cellulitis. Blood cultures should be obtained, but they are usually negative. Most patients respond to empirical therapy with broad-spectrum intravenous antibiotics. Occasionally, orbital cellulitis follows an overwhelming course, with massive proptosis, blindness, septic cavernous sinus thrombosis, and meningitis. To avert this disaster, orbital cellulitis should be managed aggressively in the early stages, with immediate antibiotic therapy and imaging of the orbits. Prompt surgical drainage of an orbital abscess or paranasal sinusitis is indicated if optic nerve function deteriorates despite antibiotics.

Tumors

Tumors of the orbit cause painless, progressive proptosis. The most common primary tumors are hemangioma, lymphangioma, neurofibroma, dermoid cyst, adenoid cystic carcinoma, optic nerve glioma, optic nerve meningioma, and benign mixed tumor of the lacrimal gland. Metastatic tumor to the orbit occurs frequently in breast carcinoma, lung carcinoma, and lymphoma. Diagnosis by fine-needle aspiration followed by urgent radiation therapy can sometimes preserve vision.

Carotid Cavernous Fistulas

With anterior drainage through the orbit these produce proptosis, diplopia, glaucoma, and corkscrew, arterialized conjunctival vessels. Direct fistulas usually result from trauma. They are easily diagnosed because of the prominent signs produced by high-flow, high-pressure shunting. Indirect fistulas, or dural arteriovenous malformations, are more likely to occur spontaneously, especially in older women. The signs are more subtle and the diagnosis is frequently missed. The combination of slight proptosis, diplopia, enlarged muscles, and an injected eye is often mistaken for thyroid ophthalmopathy. A bruit heard upon auscultation of the head, or reported by the patient, is a valuable diagnostic clue. Imaging shows an enlarged superior ophthalmic vein in the orbits. Carotid cavernous shunts can be eliminated by intravascular embolization.

Ptosis

Blepharoptosis

This is an abnormal drooping of the eyelid. Unilateral or bilateral ptosis can be congenital, from dysgenesis of the levator palpebrae superioris, or from abnormal insertion of its aponeurosis into the eyelid. Acquired ptosis can develop so gradually that the patient is unaware of the problem. Inspection of old photographs is helpful in dating the onset. A history of prior trauma, eye surgery, contact lens use, diplopia, systemic symptoms (e.g., dysphagia or peripheral muscle weakness), or a family history of ptosis should be sought. Fluctuating ptosis that worsens late in the day is typical of myasthenia gravis. Examination should focus upon evidence for proptosis, eyelid masses or deformities, inflammation, pupil inequality, or limitation of motility. The width of the

palpebral fissures is measured in primary gaze to quantitate the degree of ptosis. The ptosis will be underestimated if the patient compensates by lifting the brow with the frontalis muscle.

Mechanical Ptosis

This occurs in many elderly patients from stretching and redundancy of eyelid skin and subcutaneous fat (dermatochalasis). The extra weight of these sagging tissues causes the lid to droop. Enlargement or deformation of the eyelid from infection, tumor, trauma, or inflammation also results in ptosis on a purely mechanical basis.

Aponeurotic Ptosis

This is an acquired dehiscence or stretching of the aponeurotic tendon, which connects the levator muscle to the tarsal plate of the eyelid. It occurs commonly in older patients, presumably from loss of connective tissue elasticity. Aponeurotic ptosis is also a frequent sequela of eyelid swelling from infection or blunt trauma to the orbit, cataract surgery, or hard contact lens usage.

Myogenic Ptosis

The causes of *myogenic ptosis* include myasthenia gravis (Chap. 366) and a number of rare myopathies that manifest with ptosis. The term *chronic progressive external ophthalmoplegia* refers to a spectrum of systemic diseases caused by mutations of mitochondrial DNA. As the name implies, the most prominent findings are symmetric, slowly progressive ptosis and limitation of eye movements. In general, diplopia is a late symptom because all eye movements are reduced equally. In the *Kearns-Sayre* variant, retinal pigmentary changes and abnormalities of cardiac conduction develop. Peripheral muscle biopsy shows characteristic "ragged-red fibers."*Oculopharyngeal dystrophy* is a distinct autosomal dominant disease with onset in middle age, characterized by ptosis, limited eye movements, and trouble swallowing. *Myotonic dystrophy* , another autosomal dominant disorder, causes ptosis, ophthalmoparesis, cataract, and pigmentary retinopathy. Patients have muscle wasting, myotonia, frontal balding, and cardiac abnormalities.

Neurogenic Ptosis

This results from a lesion affecting the innervation to either of the two muscles that open the eyelid: Müller's muscle or the levator palpebrae superioris. Examination of the pupil helps to distinguish between these two possibilities. In Horner's syndrome, the eye with ptosis has a smaller pupil and the eye movements are full. In an oculomotor nerve palsy, the eye with the ptosis has a larger, or a normal, pupil. If the pupil is normal but there is limitation of adduction, elevation, and depression, a pupil-sparing oculomotor nerve palsy is likely (see next section). Rarely, a lesion affecting the small, central subnucleus of the oculomotor complex will cause bilateral ptosis with normal eye movements and pupils.

Double Vision

The first point to clarify is whether diplopia persists in either eye after covering the fellow eye. If it does, the diagnosis is monocular diplopia. The cause is usually intrinsic to the eye and therefore has no dire implications for the patient. Corneal aberrations (e.g., keratoconus, pterygium), uncorrected refractive error, cataract, or foveal traction may give rise to monocular diplopia. Occasionally it is a symptom of malingering or psychiatric disease. Diplopia alleviated by covering one eye is binocular diplopia and is caused by disruption of ocular alignment. Inquiry should be made into the nature of the double vision (purely side-by-side versus partial vertical displacement of images), mode of onset, duration, intermittency, diurnal variation, and associated neurologic or systemic symptoms. If the patient has diplopia while being examined, motility testing should reveal a deficiency corresponding to the patient's symptoms. However, subtle limitation of ocular excursions is often difficult to detect. For example, a patient with a slight left abducens nerve paresis may appear to have full eye movements, despite a complaint of horizontal diplopia upon looking to the left. In this situation, the cover test provides a more sensitive method for demonstrating the ocular misalignment. It should be conducted in primary gaze, and then with the head turned and tilted in each direction. In the above example, a cover test with the head turned to the right will maximize the fixation shift evoked by the cover test.

Occasionally, a cover test performed in an asymptomatic patient during a routine examination will reveal an ocular deviation. If the eye movements are full and the ocular misalignment is equal in all directions of gaze (concomitant deviation), the diagnosis is strabismus. In this condition, which affects about 1% of the population, fusion is disrupted in infancy or early childhood. To avoid diplopia, vision is suppressed from the nonfixating eye. In some children, this leads to impaired vision (amblyopia, or "lazy" eye) in the deviated eye.

Binocular diplopia occurs from a wide range of processes: infectious, neoplastic, metabolic, degenerative, inflammatory, and vascular. One must decide if the diplopia is neurogenic in origin or due to restriction of globe rotation by local disease in the orbit. Orbital pseudotumor, myositis, infection, tumor, thyroid disease, and muscle entrapment (e.g., from a blowout fracture) cause restrictive diplopia. The diagnosis of restriction is usually made by recognizing other associated signs and symptoms of local orbital disease in conjunction with imaging.

Myasthenia Gravis

See also Chap. 366. This is a major cause of diplopia. The diplopia is often intermittent, variable, and not confined to any single ocular motor nerve distribution. The pupils are always normal. Fluctuating ptosis may be present. Many patients have a purely ocular form of the disease, with no evidence of systemic muscular weakness. The diagnosis can be confirmed by an intravenous edrophonium injection or by an assay for

antiacetylcholine receptor antibodies. Negative results from these tests do not exclude the diagnosis. *Botulism* from food or wound poisoning can mimic ocular myasthenia.

After restrictive orbital disease and myasthenia gravis are excluded, a lesion of a cranial nerve supplying innervation to the extraocular muscles is the most likely cause of binocular diplopia.

Oculomotor Nerve

The third cranial nerve innervates the medial, inferior, and superior recti; inferior oblique; levator palpebrae superioris; and the iris sphincter. Total palsy of the oculomotor nerve causes ptosis, a dilated pupil, and leaves the eye "down and out" because of the unopposed action of the lateral rectus and superior oblique. This combination of findings is obvious. More challenging is the diagnosis of an early or partial oculomotor nerve palsy. In this setting, any combination of ptosis, pupil dilation, and weakness of the eye muscles supplied by the oculomotor nerve may be encountered. Frequent serial examinations during the evolving phase of the palsy and a high index of suspicion help ensure that the diagnosis is not missed. The advent of an oculomotor nerve palsy with any degree of pupil involvement in an otherwise healthy patient, especially when accompanied by pain, raises the specter of a circle of Willis aneurysm. If an MR imaging shows no compressive lesion, an arteriogram must be considered to rule out an aneurysm of either the posterior communicating artery or the basilar artery. If the pupil is entirely normal, with all other components of an oculomotor palsy present, aneurysm is so rare that an angiogram is seldom indicated.

A lesion of the oculomotor nucleus in the rostral midbrain produces signs that differ from those caused by a lesion of the nerve itself. There is bilateral ptosis because the levator muscle is innervated by a single central subnucleus. There is also weakness of the contralateral superior rectus, because it is supplied by the oculomotor nucleus on the other side. Occasionally both superior recti are weak. Isolated nuclear oculomotor palsy is rare. Usually neurologic examination reveals additional signs to suggest brainstem damage from infarction, hemorrhage, tumor, or infection.

Injury to structures surrounding fascicles of the oculomotor nerve descending through the midbrain has given rise to a number of classic eponymic designations. In *Nothnagel's syndrome*, injury to the superior cerebellar peduncle causes ipsilateral oculomotor palsy and contralateral cerebellar ataxia. In *Benedikt's syndrome*, injury to the red nucleus results in ipsilateral oculomotor palsy and contralateral tremor, chorea, and athetosis. *Claude's syndrome* incorporates features of both the aforementioned syndromes, by injury to both the red nucleus and the superior cerebellar peduncle. Finally, in *Weber's syndrome* , injury to the cerebral peduncle causes ipsilateral oculomotor palsy with contralateral hemiparesis.

In the subarachnoid space the oculomotor nerve is vulnerable to aneurysm, meningitis, tumor, infarction, and compression. In cerebral herniation the nerve becomes trapped between the edge of the tentorium and the uncus of the temporal lobe. Oculomotor palsy

can also occur from midbrain torsion and hemorrhages during herniation. In the cavernous sinus, oculomotor palsy arises from carotid aneurysm, carotid cavernous fistula, cavernous sinus thrombosis, tumor (pituitary adenoma, meningioma, metastasis), herpes zoster infection, and the Tolosa-Hunt syndrome.

The etiology of an isolated, pupil-sparing oculomotor palsy often remains an enigma, even after neuroimaging and extensive laboratory testing. Most cases are thought to result from microvascular infarction of the nerve, somewhere along its course from the brainstem to the orbit. Usually the patient complains of pain. Diabetes, hypertension, and vascular disease are major risk factors. Spontaneous recovery over a period of months is the rule. If this fails to occur, or if new findings develop, the diagnosis of microvascular oculomotor nerve palsy should be reconsidered. Aberrant regeneration is common when the oculomotor nerve is injured by trauma or compression (tumor, aneurysm). Miswiring of sprouting fibers to the levator muscle and the rectus muscles results in elevation of the eyelid upon downgaze or adduction. The pupil also constricts upon attempted adduction, elevation, or depression of the globe. Aberrant regeneration is not seen after oculomotor palsy from microvascular infarct and hence vitiates that diagnosis.

Trochlear Nerve

The fourth cranial nerve originates in the midbrain, just caudal to the oculomotor nerve complex. Fibers exit the brainstem dorsally and cross to innervate the contralateral superior oblique. The principal actions of this muscle are to depress and to intort the globe. A palsy therefore results in hypertropia and excyclotorsion. The cyclotorsion is seldom noticed by patients. Instead, they complain of vertical diplopia, especially upon reading or looking down. The vertical diplopia is also exacerbated by tilting the head toward the side with the muscle palsy, and alleviated by tilting it away. This "head tilt test" is a cardinal diagnostic feature.

Isolated trochlear nerve palsy occurs from all the causes listed above for the oculomotor nerve, except aneurysm. The trochlear nerve is particularly apt to suffer injury after closed head trauma. The free edge of the tentorium is thought to impinge upon the nerve during a concussive blow. Most isolated trochlear nerve palsies are idiopathic and hence diagnosed by exclusion as "microvascular." Spontaneous improvement occurs over a period of months in most patients. A base-down prism (conveniently applied to the patient's glasses as a stick-on Fresnel lens) may serve as a temporary measure to alleviate diplopia. If the palsy does not resolve, the eyes can be realigned by weakening the inferior oblique muscle.

Abducens Nerve

The sixth cranial nerve innervates the lateral rectus muscle. A palsy produces horizontal diplopia, worse on gaze to the side of the lesion. A nuclear lesion has different consequences, because the abducens nucleus contains interneurons that project via the medial longitudinal fasciculus to the medial rectus subnucleus of the contralateral oculomotor complex. Therefore, an abducens nuclear lesion produces a complete lateral

gaze palsy, from weakness of both the ipsilateral lateral rectus and the contralateral medial rectus. *Foville's syndrome* following dorsal pontine injury includes lateral gaze palsy, ipsilateral facial palsy, and contralateral hemiparesis incurred by damage to descending corticospinal fibers. *Millard-Gubler syndrome* from ventral pontine injury is similar, except for the eye findings. There is lateral rectus weakness only, instead of gaze palsy, because the abducens fascicle is injured rather than the nucleus. Infarct, tumor, hemorrhage, vascular malformation, and multiple sclerosis are the most common etiologies of brainstem abducens palsy.

After leaving the ventral pons, the abducens nerve runs forward along the clivus to pierce the dura at the petrous apex, where it enters the cavernous sinus. Along its subarachnoid course it is susceptible to meningitis, tumor (meningioma, chordoma, carcinomatous meningitis), subarachnoid hemorrhage, trauma, and compression by aneurysm or dolichoectatic vessels. At the petrous apex, mastoiditis can produce deafness, pain, and ipsilateral abducens palsy (*Gradenigo's syndrome*). In the cavernous sinus, the nerve can be affected by carotid aneurysm, carotid cavernous fistula, tumor (pituitary adenoma, meningioma, nasopharyngeal carcinoma), herpes infection, and Tolosa-Hunt syndrome.

Unilateral or bilateral abducens palsy is a classic sign of raised intracranial pressure. The diagnosis can be confirmed if papilledema is observed on fundus examination. The mechanism is still debated but is probably related to rostral-caudal displacement of the brainstem. The same phenomenon accounts for abducens palsy from low intracranial pressure (e.g., after lumbar puncture, spinal anesthesia, or spontaneous dural cerebrospinal fluid leak).

Treatment of abducens palsy is aimed at prompt correction of the underlying cause. However, the cause remains obscure in many instances, despite diligent evaluation. As mentioned above for isolated trochlear or oculomotor palsy, most cases are assumed to represent microvascular infarcts because they often occur in the setting of diabetes or other vascular risk factors. Some cases may develop as a postinfectious mononeuritis (e.g., following a viral flu). Patching one eye or applying a temporary prism will provide relief of diplopia until the palsy resolves. If recovery is incomplete, eye muscle surgery can nearly always realign the eyes, at least in primary position. A patient with an abducens palsy that fails to improve should be reevaluated for an occult etiology (e.g., chordoma, carcinomatous meningitis, carotid cavernous fistula, myasthenia gravis).

Multiple Ocular Motor Nerve Palsies

These should not be attributed to spontaneous microvascular events affecting more than one cranial nerve at a time. This remarkable coincidence does occur, especially in diabetic patients, but the diagnosis is made only in retrospect after exhausting all other diagnostic alternatives. Neuroimaging should focus on the cavernous sinus, superior orbital fissure, and orbital apex, where all three ocular motor nerves are in close proximity. In the diabetic or compromised host, fungal infection (*Aspergillus*, Mucorales, *Cryptococcus*) is a frequent cause of multiple nerve palsies. In the patient with systemic malignancy, carcinomatous meningitis is a likely diagnosis. Cytologic examination may

be negative despite repeated sampling of the cerebrospinal fluid. The cancer-associated Lambert-Eaton myasthenic syndrome can also produce ophthalmoplegia. Giant cell (temporal) arteritis occasionally manifests as diplopia from ischemic palsies of extraocular muscles. Fisher syndrome, an ocular variant of Guillain-Barré, can produce ophthalmoplegia with areflexia and ataxia. Often the ataxia is mild, and the areflexia is overlooked because the physician's attention is focused upon the eyes. Antiganglioside antibodies (GQ1b) can be detected in about 50% of cases.

Supranuclear Disorders of Gaze

These are often mistaken for multiple ocular motor nerve palsies. For example, Wernicke's encephalopathy can produce nystagmus and a partial deficit of horizontal and vertical gaze that mimics a combined abducens and oculomotor nerve palsy. The disorder occurs in malnourished or alcoholic patients and can be reversed by thiamine. Infarct, hemorrhage, tumor, multiple sclerosis, encephalitis, vasculitis, and Whipple's disease are other important causes of supranuclear gaze palsy. Disorders of vertical gaze, especially downwards saccades, are an early feature of progressive supranuclear palsy. Smooth pursuit is affected later in the course of the disease. Parkinson's disease, Huntington's chorea, and olivopontocerebellar degeneration can also affect vertical gaze.

The *frontal eye field* of the cerebral cortex is involved in generation of saccades to the contralateral side. After hemispheric stroke, the eyes usually deviate towards the lesioned side because of the unopposed action of the frontal eye field in the normal hemisphere. With time, this deficit resolves. Seizures generally have the opposite effect: the eyes deviate conjugately away from the irritative focus. *Parietal lesions* disrupt smooth pursuit of targets moving toward the side of the lesion. Bilateral parietal lesions produce *Balint's syndrome* , characterized by impaired eye-hand coordination (optic ataxia), difficulty initiating voluntary eye movements (ocular apraxia), and visuospatial disorientation (simultanagnosia).

Horizontal Gaze

Descending cortical inputs mediating horizontal gaze ultimately converge at the level of the pons. Neurons in the paramedian pontine reticular formation are responsible for controlling conjugate gaze toward the same side. They project directly to the ipsilateral abducens nucleus. A lesion of either the paramedian pontine reticular formation or the abducens nucleus causes an ipsilateral conjugate gaze palsy. Lesions at either locus produce nearly identical clinical syndromes, with the following exception: vestibular stimulation (oculocephalic maneuver or caloric irrigation) will succeed in driving the eyes conjugately to the side in a patient with a lesion of the paramedian pontine reticular formation, but not in a patient with a lesion of the abducens nucleus.

Internuclear Ophthalmoplegia

This results from damage to the medial longitudinal fasciculus ascending from the abducens nucleus in the pons to the oculomotor nucleus in the midbrain (hence,

"internuclear"). Damage to fibers carrying the conjugate signal from abducens interneurons to the contralateral medial rectus motoneurons results in a failure of adduction on attempted lateral gaze. For example, a patient with a left internuclear ophthalmoplegia will have slowed or absent adducting movements of the left eye. A patient with bilateral injury to the medial longitudinal fasciculus will have bilateral internuclear ophthalmoplegia. Multiple sclerosis is the most common cause, although tumor, stroke, trauma, or any brainstem process may be responsible. *One-and-a-half syndrome* is due to a combined lesion of the medial longitudinal fasciculus and the abducens nucleus on the same side. The patient's only horizontal eye movement is abduction of the eye on the other side.

Vertical Gaze

This is controlled at the level of the midbrain. The neuronal circuits affected in disorders of vertical gaze are not fully elucidated, but lesions of the rostral interstitial nucleus of the medial longitudinal fasciculus and the interstitial nucleus of Cajal cause supranuclear paresis of upgaze, downgaze, or all vertical eye movements. Distal basilar artery ischemia is the most common etiology. *Skew deviation* refers to a vertical misalignment of the eyes, usually constant in all positions of gaze. The finding has poor localizing value because skew deviation has been reported after lesions in widespread regions of the brainstem and cerebellum.

Parinaud's Syndrome

Also known as dorsal midbrain syndrome, this is a distinct supranuclear vertical gaze disorder from damage to the posterior commissure. It is a classic sign of hydrocephalus from aqueductal stenosis. Pineal region tumors, cysticercosis, and stroke also cause Parinaud's syndrome. Features include loss of upgaze (and sometimes downgaze), convergence-retraction nystagmus on attempted upgaze, downwards ocular deviation ("setting sun" sign), lid retraction (Collier's sign), skew deviation, pseudoabducens palsy, and light-near dissociation of the pupils.

Nystagmus

This is a rhythmical oscillation of the eyes, occurring physiologically from vestibular and optokinetic stimulation or pathologically in a wide variety of diseases (Chap. 20). Abnormalities of the eyes or optic nerves, present at birth or acquired in childhood, can produce a complex, searching nystagmus with irregular pendular (sinusoidal) and jerk features. This nystagmus is commonly referred to as *congenital sensory nystagmus*. It is a poor term, because even in children with congenital lesions, the nystagmus does not appear until several months of age. *Congenital motor nystagmus* , which looks similar to congenital sensory nystagmus, develops in the absence of any abnormality of the sensory visual system. Visual acuity is also reduced in congenital motor nystagmus, probably by the nystagmus itself, but seldom below a level of 20/200.

Jerk Nystagmus

This is characterized by a slow drift off the target, followed by a fast corrective saccade. By convention, the nystagmus is named after the quick phase. Jerk nystagmus can be downbeat, upbeat, horizontal (left or right), and torsional. The pattern of nystagmus may vary with gaze position. Some patients will be oblivious to their nystagmus. Others will complain of blurred vision, or a subjective, to-and-fro movement of the environment (oscillopsia) corresponding to their nystagmus. Fine nystagmus may be difficult to see upon gross examination of the eyes. Observation of nystagmoid movements of the optic disc on ophthalmoscopy is a sensitive way to detect subtle nystagmus.

Gaze-Evoked Nystagmus

This is the most common form of jerk nystagmus. When the eyes are held eccentrically in the orbits, they have a natural tendency to drift back to primary position. The subject compensates by making a corrective saccade to maintain the deviated eye position. Many normal patients have mild gaze-evoked nystagmus. Exaggerated gaze-evoked nystagmus can be induced by drugs (sedatives, anticonvulsants, alcohol); muscle paresis; myasthenia gravis; demyelinating disease; and cerebellopontine angle, brainstem, and cerebellar lesions.

Vestibular Nystagmus

Vestibular nystagmus results from dysfunction of the labyrinth (Ménière's disease), vestibular nerve, or vestibular nucleus in the brainstem. Peripheral vestibular nystagmus often occurs in discrete attacks, with symptoms of nausea and vertigo. There may be associated tinnitus and hearing loss. Sudden shifts in head position may provoke or exacerbate symptoms.

Downbeat Nystagmus

Downbeat nystagmus occurs from lesions near the craniocervical junction (Chiari malformation, basilar invagination). It has also been reported in brainstem or cerebellar stroke, lithium or anticonvulsant intoxication, alcoholism, and multiple sclerosis. *Upbeat nystagmus* is associated with damage to the pontine tegmentum, from stroke, demyelination, or tumor.

Opsoclonus

This rare, dramatic disorder of eye movements consists of bursts of consecutive saccades (saccadomania). When the saccades are confined to the horizontal plane, the term *ocular flutter* is preferred. It can occur from viral encephalitis, trauma, or a paraneoplastic effect of neuroblastoma, breast carcinoma, and other malignancies. It has also been reported as a benign, transient phenomenon in otherwise healthy patients.

Further Reading

AREDS Report No. 8: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. Arch Ophthalmol 119:1417, 2001

Alaedini A et al: Detection of anti-ganglioside antibodies in Guillain-Barre syndrome and its variants by the agglutination assay. J Neurol Sci 196:41, 2002 [PMID: 11959155]

Albert DM, Jakobiec FA (eds): *Principles and Practice of Ophthalmology*, 2d ed. Philadelphia, Saunders, 2000

Beck RW et al: A randomized controlled trial of corticosteroids in the treatment of acute optic neuritis. N Engl J Med 326:581, 1992 [PMID: 1734247]

Beck RW et al: Interferon beta-la for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol 51:481, 2002 [PMID: 11921054]

Benavente O et al: Prognosis after transient monocular blindness associated with carotid artery stenosis. N Engl J Med 345:1084, 2001 [PMID: 11596587]

Gass JD: *Stereoscopic Atlas of Macular Diseases*, 4th ed. St. Louis, Mosby, 1996

Gold DH, Weingeist TA (eds): *The Eye in Systemic Disease*. Philadelphia, Lippincott, 1990

Hatter S et al: Melanopsin-containing retinal ganglion cells: Architecture, projections, and intrinsic photosensitivity. Science 295: 1065, 2002

Leibowitz HM (eds): *Corneal Disorders. Clinical Diagnosis and Management*. Philadelphia, Saunders, 1998

Leibowitz HM: The red eye. N Engl J Med 343:345, 2000 [PMID: 10922425]

Leigh RJ, Zee DS: *The Neurology of Eye Movements*, 3d ed. Oxford, Oxford Univ Press, 1999

Miller NR, Newman NJ: *Walsh and Hoyt's Clinical Neuroophthalmology*, 5th ed. Baltimore, Williams & Wilkins, 1998

Negi A, Vernon SA: An overview of the eye in diabetes. JR Soc Med 96:266, 2003 [PMID: 12782689]

Neitz M, Neitz J: Molecular genetics of color vision and color vision defects. Arch Ophthalmol 118:691, 2000 [PMID: 10815162]

Singh G et al: A mitochondrial DNA mutation as a cause of Leber's hereditary optic neuropathy. N Engl J Med 320:1300, 1989 [PMID: 2566116]

Solomon R, Donnenfeld ED: Recent advances and future frontiers in treating age-related cataracts. JAMA 290:248, 2003 [PMID: 12851280]

Spencer WH (ed): *Ophthalmic Pathology. An Atlas and Textbook*, 4th ed. Philadelphia, Saunders, 1996

Tayebeh R et al: Adult-onset primary open-angle glaucoma caused by mutations in optineurin. Science 295:1077, 2002

Trobe JD: *The Neurology of Vision*, Univ Michigan Med School (Contemporary Neurology Series 60), 2001

Vaughn D et al: *General Ophthalmology*, 15th ed. Norwalk, Appleton & Lange, 1999